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# THE EFFECT OF DUODENAL STIMULATION IN MAN UPON ALIMENTARY AND ADRENALIN HYPERGLYCEMIA *

By HARRY SHAY, M.D., J. GERSHON-COHEN, M.D., D.Sc. (Med.), and SAMUEL S. FELS, LL.D., *Philadelphia, Pennsylvania*

As early as 1825, Leuret and Lassaigne [33] from studies on the horse and dog wrote that the causes which determined the secretion of pancreatic juice were analogous to those which influenced the outflow of saliva. From the application of various substances to the orifice of the pancreatic duct they concluded that weak acids, especially, caused an abundant flow of pancreatic juice. Later, in a discussion of the physiology of the intestine, they made the pertinent suggestion that the chyme, since it was constantly acid, must enjoy the same property upon its passage from the stomach into the intestines. One must remember that this was written in the first year following the discovery of hydrochloric acid in the gastric juice by the English chemist Prout,[43] a fact which was still unknown to Leuret and Lassaigne [33] as is obvious from their discussion of the composition of gastric juice. It should be recalled too, that it was in 1825 that Beaumont [2] succeeded in healing sufficiently the gunshot wound of Alexis St. Martin to allow observations that were to give us, eight years later, the introduction to modern gastric physiology. Nearly 70 years were to elapse, however, before Bekker [3] and Dolinski [11] would decide in Pavlov's laboratory that acids applied to the duodenal mucosa provoke a flow of pancreatic juice; and nearly another decade before Bayliss and Starling [1] would show this effect to be due to a humoral mechanism. The splendid contributions of Leuret and Lassaigne [33] seem to be almost forgotten.

The further demonstration by Bayliss and Starling [1] that the injection of acid extracts of intestinal mucosa into normal animals could stimulate the external pancreatic secretion prompted an investigation into the efficacy of these extracts in the production of the internal secretion. It was soon

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From the Samuel S. Fels Research Fund and the Gastro-Intestinal Division of Medical Service—I. Mt. Sinai Hospital, Philadelphia, Pa.

recognized that the intravenous injection of these extracts produced not only stimulation of the external pancreatic secretion, but also a vaso-depressive effect and a diminution of blood sugar. The practical value of the latter action was obvious. During the 35 years since the crucial experiments of Bayliss and Starling repeated efforts have been made to explain the hypoglycemic action of duodenal extracts; and there have been numerous experimental applications of such preparations in the treatment of clinical diabetes. These attempts, from the first failure of Spriggs [49] to influence internal pancreatic secretion with duodenal extracts, to the recent success of La Barre [28] in lowering the blood sugar in depancreatized dogs by the duodenal instillation of hydrochloric acid, have added an extensive and provocative chapter to the physiology of the gastro-duodenal segment.

In the same year (1906) that Moore, Edie and Abrams reported the first seemingly good results from the use of the hydrochloric acid extracts of the duodenum and upper jejunum in clinical diabetes, C. Workman [55] found evidence of changes in the duodenal mucosa in diabetes mellitus. He reported hypertrophy of the duodenal mucosa and of the valvulae conniventes in 10 of 21 cases. However, the most intensive and productive investigations in the field have been made in the past 15 years. These investigations have yielded much contradictory evidence. There have been investigators, who, in turn, have attributed a hyperglycemic effect, and a hypoglycemic effect to the glycemic factor, while still other investigators found it productive of both. These variations, of course, are explicable. Much thought, too, has been given as to whether the hypoglycemic factor in duodenal extracts represented an extract of insulin from the intestine; a hormone which stimulated the islet cell; an agent which was itself, capable of increasing glucose utilization; or an agent which embodied the two last properties. These studies reached their climax when the hypoglycemic agent in duodenal extracts was isolated from the secretagogic factor and when it was proved that this agent was effective, administered orally or parenterally, in the reduction of blood sugars in depancreatized animals. Upon examination, these investigations point to a clear relationship of a duodenal mechanism to the blood sugar control, at least in so far as alimentary hyperglycemia is concerned. These conclusions have resulted mainly from animal experimentation. Although suggestive data have been reported for man by Macallum and his associates,[31, 32, 35] by Italian investigators [4, 7, 38, 54] and by Duncan and his co-workers,[12] no real existence of a similar mechanism in the human being has been demonstrated. Since it is increasingly apparent that clinical diabetes is not exclusively the expression of primary islet damage, and since there are experimental results which suggest disturbed duodenal function as a factor, the investigation of the hypoglycemic duodenal mechanism in man is of especial interest.

## Experimental Method

The investigation of this problem came about quite by accident. Shay and Gershon-Cohen [48] showed in their studies that by duodenal stimulation the pylorus could be effectively closed for varying periods. This method was applied to a study of the problem of gastric absorption by the intact human stomach. The need to explain the results of the study of glucose absorption led to a consideration of the present problem.

Six patients—one diabetic—who after study showed no evidence of any gastrointestinal disease, were selected. A seventh case was a severe diabetic with a calcified pancreas. After a 12 hour fast period the duodenum was intubated in the usual manner with an Einhorn tube. The location of the tip of the tube was determined roentgenologically. There were then instilled into the duodenum various solutions whose effectiveness in producing continuous pyloric closure had already been established. These solutions were instilled at the rate of 60 to 80 drops per minute, using a Murphy drip bulb to regulate the flow. The stimulants employed were 0.47 per cent hydrochloric acid, olive oil, 1 and 7 per cent sodium bicarbonate, normal saline, and 5 per cent sodium chloride, as well as 40 to 50 per cent solutions of glucose.

Five minutes after the duodenal instillation was begun, 225 c.c. of approximately 40 per cent glucose, mixed with two ounces of barium sulphate were ingested. The instillation was continued for 30 minutes. Fluoroscopic observations and roentgenographic records were made at frequent intervals in order to make certain that none of the gastric contents had left the stomach. To verify this fact, the instillation was interrupted at 10 and 25 minutes to make five minute collections of the duodenal contents. It had been shown previously that effective closure of the pylorus would be maintained in spite of such short interruptions to collect duodenal contents. Since the glucose in the gastric contents was of such high concentration, a negative sugar reaction in the duodenal fractions collected for a 10 minute period of the total 30 minute test would be strong additional evidence that none of the gastric contents had passed the pylorus. All experiments which either showed barium in the duodenum or gave a positive sugar reaction in the duodenal contents were rejected. Blood and urine samples for sugar determinations were collected prior to (fasting) and at 15 and 30 minute intervals after ingestion of the glucose. At the end of the 30 minute period the duodenal stimulation was stopped, and the tube rapidly pulled back under fluoroscopic control so that the tip rested in the antrum. The stomach was then completely emptied under fluoroscopic control. This was followed by gastric lavage. The test subject ingested a measured amount of water which was then removed by way of the tube. This was repeated three times. A comparison of the volumes of the ingested lavage with that recovered, shows how completely the stomach may be emptied of liquid contents.

The following table demonstrates the quantities of gastric lavage fluid and their glucose contents recovered after the stomach has been emptied of the remainder of the glucose meal, at the end of the 30 minute test period:

TABLE I

| | Vol. ingested c.c. | Vol. recovered c.c. | Per cent glucose | Total glucose gm. |
|---|---|---|---|---|
| 1st lavage..... | 240 | 235 | 1.0 | 2.35 |
| 2d " ..... | 240 | 240 | 0.33 | 0.8 |
| 3d " ..... | 240 | 235 | 0.13 | 0.3 |
| 1st lavage..... | 250 | 240 | 1.0 | 2.4 |
| 2d " ..... | 250 | 215 | 0.4 | 0.9 |
| 3d " ..... | 250 | 205 | 0.2 | 0.3 |
| 1st lavage..... | 225 | 215 | 1.2 | 2.7 |
| 2d " ..... | 225 | 225 | 0.22 | 0.5 |
| 3d " ..... | 225 | 235 | 0.1 | 0.23 |

When the total glucose figures of the lavages are compared with the concentration of glucose in the stomach at the end of the test period the result is especially indicative of how completely the gastric contents had been removed before the lavages. Thus the glucose concentration in the recovered meals in the three instances cited, were 19.3, 25.0 and 18.5 per cent respectively. The concentrations of glucose in the meals ingested were 35.7, 38.5 and 40 per cent. Allowing for the small, but not serious, error of the method used for recovering the lavage fluid, it will be seen that these recoveries may be considered essentially quantitative. Such practically quantitative recovery of the lavage fluids indicates, too, how pyloric closure may be maintained for a variable period after the duodenal stimulant has been stopped. The recovered meal at the end of half an hour, as well as all the lavage specimens, were freed of barium sulphate by centrifugation. The barium sulphate was then washed and recentrifuged three times with 25 c.c. portions of water in order completely to recover all glucose solutions. Quantitative determinations of the glucose contents of the recovered meal and washes were made by Benedict's method. Blood sugar was determined by the Folin Wu method. The urine specimens were tested for glucose by the Benedict qualitative method. Since two ounces of barium sulphate were mixed with the ingested glucose meal, and since the barium was removed from the recovered meal before glucose determinations were made, it was necessary to make certain that no adsorption of glucose by the barium sulphate had occurred. Therefore quantities of glucose solution and barium sulphate similar to those used in the studies were mixed, after having previously determined the glucose concentration of the solution. This mixture was placed in a constant temperature water bath at 38° C., for 30 minutes, after which the barium was removed by centrifugation, treated

as above, and the total quantity of glucose left in the solution measured. No adsorption of glucose by the barium sulphate occurred.

## Results and Discussion

At the half-hour period after the ingestion of approximately 90 grams of glucose in a highly concentrated solution (40 per cent), with the pylorus effectively closed, there was a loss of glucose from the stomach in amounts varying from 11.6 to 31.5 grams (table 2). Considering the conditions of

Table II

Showing the range of absorption of glucose by the stomach after its ingestion in high concentration (37 to 43%) and the usual negligible variation of blood sugar level resulting from simultaneous duodenal stimulation. Illustrative examples.

| Duodenal Instillation | Total Glucose Ingested | Total Glucose Recovered | Glucose Absorbed by Stomach | Blood Sugar mg./100 c.c. | | |
|---|---|---|---|---|---|---|
| | | | | Fasting | 15 min. | 30 min. |
| 0.47% HCl | 97.9 gm. | 78.6 gm. | 19.3 gm. | 95.0 | 92.0 | 97.0 |
| 0.47% HCl | 90.0 " | 58.5 " | 31.5 " | 175.0 | 160.0 | 171.0 |
| 0.47% HCl | 90.0 " | 78.4 " | 11.6 " | 78.4 | 77.1 | 81.3 |
| 0.47% HCl | 93.4 " | 68.8 " | 24.8 " | 97.0 | 97.5 | 97.0 |
| 7% $NaHCO_3$ | 96.2 " | 79.6 " | 16.6 " | 80.2 | 77.8 | 86.6 |
| Olive oil | 86.6 " | 67.0 " | 19.6 " | 94.0 | 97.0 | 98.0 |
| Olive oil | 93.4 " | 64.3 " | 29.1 " | 85.1 | 86.2 | 89.0 |
| 7% $NaHCO_3$ | 96.2 " | 74.3 " | 21.9 " | 75.8 | 79.6 | 82.4 |
| 5% NaCl | 92.3 " | 71.4 " | 20.9 " | 80.2 | 77.2 | 86.1 |
| 5% NaCl | 80.8 " | 66.2 " | 14.6 " | 68.1 | 72.2 | 75.0 |

the experiments, only one conclusion was possible: *gastric absorption of glucose had occurred.* The finding that was difficult to explain, however, was that seen in the blood sugar readings. It may be noted, in table 2, that the changes in blood sugar concentration after the ingestion of the glucose meal in the 15 to 30 minute blood specimens *are negligible* when compared with the fasting blood sugar level. The largest rises seen in the 10 examples cited in table 1 occur in the eighth and last cases, in which the rises in blood sugar concentration were 6.6 mg. and 6.9 mg. respectively, in the half hour blood specimens. During the test period there was a loss of 21.9 grams and of 14.8 grams of glucose from the stomach. Even the largest changes in blood sugar concentration would fall practically within the limits of error of the method for glucose determination.

These observations became of particular interest when the blood sugar concentrations in the same patients were determined after the direct duodenal instillation of quantities of sugar in isotonic solution* similar to

* The duodenal instillations of similar amounts of glucose to that absorbed in the gastric experiments were made in isotonic concentration, because of the experimental evidence of Ravdin, Johnston and Morrison [44] in dogs, that the concentration of glucose in the upper intestine was around isotonicity regardless of the concentration of the solution instilled into the stomach.

those which had been absorbed from the stomach. These quantities of glucose, when instilled directly into the duodenum, in all cases produced *a definite rise in blood sugar at 15 and 30 minute intervals.* The rise in blood sugar resulting from this procedure was often comparable to that seen, at the same intervals, after the ingestion of the 40 per cent glucose meal in the absence of duodenal stimulation, although larger quantities of glucose had left the stomach under these conditions. (Charts 1, 4, 6.)

Charts 6 and 7 illustrate results obtained in two diabetic patients. It will be seen that they present entirely different pictures in their response to duodenal stimulation. Chart 6 represents the results obtained in an uncomplicated diabetic in which the response to duodenal stimulation during glucose absorption from the stomach is seen to parallel the findings in normal individuals. Thus, after the ingestion of 225 c.c. of 38.5 per cent glucose by mouth and without duodenal stimulation, 38.6 grams disappeared from the stomach in 30 minutes. The blood sugar concentration under these conditions changed from a fasting level of 195.5 mg. per 100 c.c. to 268 mg., a rise of 72.5 mg. per 100 c.c. at the end of 30 minutes. Twenty-five grams of glucose in isotonic solution, instilled into the duodenum of the same patient on another day, produced a similar change in blood sugar concentration during a similar period. Thus, starting with a fasting sugar of 180 mg. per 100 c.c. of blood, the sugar concentration rose to 260 mg. per 100 c.c. in the following half hour, a rise in concentration of 80 mg. per 100 c.c. of blood. Like the non-diabetic, this patient showed *no appreciable change from the fasting blood sugar level while glucose was absorbed from the stomach and the duodenum was stimulated simultaneously.* Although glucose was absorbed in amounts that should have produced a marked rise in blood sugar, one sees from curves C and D, chart 6, that no such rise occurred.

Chart 7, on the contrary, presents an entirely different picture. Here there is no evidence of enhanced glucose utilization accompanying the duodenal stimulation. Starting with a fasting blood sugar of 260 mg. per 100 c.c., there is a rise to 305 mg. thirty minutes after the duodenal instillation of 25 grams of glucose in isotonic solution, a change of 45 mg. per 100 c.c. On another day the same patient, following the ingestion of 225 c.c. of 41.7 per cent glucose and the simultaneous duodenal instillation of 0.47 per cent hydrochloric acid, showed a loss from the stomach of 27.6 grams of glucose in the following half hour. *The blood sugar concentration changed from a fasting level of 277 mg. per 100 c.c. to 308 mg., a change in concentration of 31 mg. per 100 c.c.*

We see, therefore, a distinct difference in the behavior of the patient represented in chart 7, from that observed in the normal and uncomplicated diabetic. The patient in chart 7 was a very severe diabetic in whom, apparently, a diffuse calcification of the pancreas had occurred. Roentgenographs showed the area corresponding to the region of the pancreas to be

studded with calcific areas, which in their aggregate had a pancreas-like distribution. The fasting blood sugar figures noted occurred in spite of a daily dosage of 80 units of insulin.

### The Effect of Hydrochloric Acid in the Duodenum upon Blood Sugar Concentration

While the possible relationship of secretin to enhanced islet activity was considered almost from its discovery, it was not until 1926 that hydrochloric acid—the provocative agent in the crucial experiment of Bayliss and Starling [1]—was shown to influence the blood sugar level. Freud and Saadi-Nazim,[15] using chloralized dogs, injected 60 to 100 c.c. of 0.5 per cent hydrochloric acid into the duodenum and studied the blood sugar concentration at intervals for two hours. All except one of the dogs so treated showed a drop in blood sugar following the acid injection. To eliminate the possibility that chloral hydrate was acting as the sugar depressant they studied the effect of the gastric instillation of similar quantities of the acid in unanesthetized dogs and obtained similar changes in blood sugar.

Two years later, Gley and Hazard [16] demonstrated that the duodenal injection of hydrochloric acid was followed by the appearance in the circulating blood of the animal of a substance which could lower the blood sugar. After making certain that a flow of pancreatic juice was produced by the duodenal injection of the acid, they removed blood from their animal, separated the serum, and injected this into the mesenteric or saphenous vein of a second dog. Testing the blood sugar of the recipient at 15 minute intervals thereafter, they found a diminution of the blood sugar, as compared with the fasting level, in five of the seven dogs so treated. This decrease amounted to more than 40 milligrams per 100 c.c. of blood in one animal. In another series of experiments, the same investigators, by anastomosing the pancreatico-duodenal vein of the donor with the splenic vein of the recipient, observed a drop in blood sugar concentration of the recipient, following the duodenal injection of the acid into the donor. Later La Barre and Ledrut [27] noted a marked reduction of blood sugar level even in the totally depancreatized animal after the injection of 0.5 to 0.8 per cent hydrochloric acid into the duodenum. Coehlo and Oliveira [6] reported reductions in blood sugar after duodenal injection of 30 cubic centimeters of tenth-normal hydrochloric acid in patients with gastrointestinal, pancreatic, and liver affections. Italian literature contains several reports in which blood sugar reduction in man was obtained with hydrochloric acid medication. Thus Boattini [4] in 1931 reported a uniform reduction in glycemia in diabetics after hydrochloric acid orally administered. This change in glycemia occurred one to two hours after the administration of the acid. Conti [7] observed similar results both from oral administration and from duodenal instillation of the acid.

Although the original observations of Freud and Saadi-Nazim [15] were

concerned with changes produced in the fasting blood sugar level of their dogs by the duodenal instillation of hydrochloric acid, most subsequent observers, and especially those who have studied the effect of hydrochloric acid on the duodenum of human beings, have been unable to change this level to any degree. Thus Boattini [4] and Conti [7] report scarcely any effect on the fasting blood sugar of the non-diabetic. Michelazzi [38] saw, in the normal human subject, a definite change in the curve of alimentary hyperglycemia produced by the acid but no appreciable variations in the fasting glycemic curve. Lucchi,[34] on the other hand, reported a reduction in the fasting glycemia in the majority of his normal subjects following the duodenal injection of 60 to 70 c.c. of 0.8 per cent hydrochloric acid.

The lack of effect upon the normal fasting blood sugar level is apparently not limited to the acid action alone. Duodenal extracts likewise have usually shown a *lack of action upon the fasting blood sugar level.* Oehme and Wimmers [39] record a temporary lowering of the fasting blood sugar in dogs and rabbits from their preparation—an effect which was less than that obtained when glucose had been administered. Heller [18] employing intestinal extracts (1929) at no time was able to cause any reduction in the fasting blood sugar values of rabbits, although the same extracts were effective, both by injection and orally, following the intravenous injection of glucose. In his later work, however, Heller [20] (1935) was able with more highly refined preparations to affect the normal blood sugar level. Laughton and Macallum [32] (1932) were unable to influence the fasting blood sugar of normal rabbits with their preparation and Duncan [12] reported similar failure in both rabbits and dogs.

If we now examine our data of charts 1, 4, and 5, we find that the instillation of hydrochloric acid in concentrations ranging around 0.45 per cent and at a speed of from 60 to 100 drops per minute invariably prevented a rise in blood sugar during the gastric absorption of glucose in amounts which would ordinarily be quite adequate to elevate the blood sugar concentration. The results shown in chart 1 will serve as an illustration. In this case the ingestion of 225 c.c. of 41.5 per cent glucose and the simultaneous duodenal instillation of 0.47 per cent hydrochloric acid at the rate of 100 drops per minute showed evidences, at the end of 30 minutes, of the gastric absorption of 20.6 grams. The blood sugar concentration during this period was virtually unchanged, the test period beginning with a fasting level of 97 mg. per 100 c.c. of blood. In the same patient, on another day, when twenty grams of glucose in isotonic solution were instilled into the fasting duodenum, the blood sugar at 15 and 30 minute intervals showed a very *sharp rise.* Starting with a fasting level of 93 mg. per 100 c.c. of blood, it rose at the 15 minute interval to 145 mg. and at 30 minutes had reached 185 mg. per 100 c.c. of blood. Chart 4 illustrates that varying the duodenal instillation of the acid between 60 and 100 drops per minute did not alter the result obtained. The data clearly indicate that the duodenal

instillation of hydrochloric acid is capable of counteracting an alimentary hyperglycemia.

It was impossible, however, in a group of 10 normal cases (table 3), to produce any material reduction of the fasting blood sugar level by the

TABLE III

Effect of Duodenal Stimulation upon Normal Fasting Blood Sugar

| Duodenal Stimulant | Blood Sugar mg./100 c.c. | | | | | |
|---|---|---|---|---|---|---|
| | F. | 15 min. | 30 min. | 45 min. | 60 min. | 90 min. |
| Case 1. No duod. tube | 73.0 | 71.4 | 66.7 | 69.0 | 67.9 | |
| Case 1. 0.47% HCl | 90.1 | 84.4 | 79.0 | 79.1 | 79.7 | 80.1 |
| Case 2. Olive oil | 76.3 | 76.3 | 74.9 | 74.7 | 69.7 | 72.8 |
| Case 3. Olive oil | 79.0 | 76.3 | 87.3 | 82.2 | 76.3 | 78.4 |
| Case 4. 0.47% HCl | 92.2 | 92.2 | 100.0 | 95.2 | 80.0 | 82.6 |
| Case 5. 0.49% HCl | 86.2 | 79.9 | 80.6 | | 84.7 | 83.1 |
| Case 6. 0.49% HCl | 83.3 | 81.3 | 80.2 | | 82.6 | |
| Case 7. 0.45% HCl | 79.7 | 78.6 | 78.7 | 77.8 | 76.9 | 76.6 |
| Case 8. 0.47% HCl | 72.4 | 70.7 | 72.2 | 74.0 | | 71.6 |
| Case 9. 5% NaCl | 88.0 | 87.8 | 84.2 | | 86.2 | |
| Case 10. 7% $NaHCO_3$ | 86.2 | 83.9 | 84.6 | 84.1 | 85.1 | |

Case 1 showed greatest change from fasting value 11.1 mg. A similar curve, however, made at same period of day without duodenal stimulant showed a change of 6.3 mg. Quantity of stimulant instilled into duodenum = 200 c.c.

duodenal instillation of any of the substances which readily prevented a rise in blood sugar during glucose absorption. The greatest change was seen in case 1, in whom after 30 minutes of continuous instillation of 0.47 per cent hydrochloric acid there was a drop in blood sugar concentration from a pre-instillation fasting level of 90.1 mg. to 79.0 mg. per 100 c.c. of blood,—a fall of 11.1 mg. While this represents a drop of 12.2 per cent from the fasting level and might be considered a change produced by the duodenal instillation, consideration must be given to the fact that the change in the other nine cases was negligible and that even case 1, when followed on another day from the same period at the same time of day, without duodenal stimulation, showed a change of 6.3 mg. of blood sugar during the same period. The blood sugar changed from 73 to 66.7 mg. of glucose per 100 c.c., a change of more than 8.6 per cent. Our results, therefore, would confirm those workers who *were unable to modify the normal fasting blood sugar level by duodenal stimulation.* The fact that similar duodenal stimulation is capable of preventing alimentary hyperglycemia, yet unable to modify the fasting blood sugar level, indicates how delicately attuned must be the mechanism concerned in the maintenance of a normal blood sugar. This is in accordance with what we know of the importance of the normal blood sugar level.

## A Consideration of the Possible Mechanism Involved in the Hypoglycemic Action of the Duodenum

In order to explain our results adequately, we must consider the ways in which the duodenum might be effective in reducing the blood sugar level. Very suggestive information may be found in the data reported from the use of duodenal extracts, as well as in the results from duodenal stimulation. The mechanism of the production of the hypoglycemic effect may be considered as possibly dependent upon:

I. Secretin;
II. An extraction of insulin from duodenal pancreatic tissue;
III. Islet stimulation by an agent originating in the duodenum;
IV. A separate duodenal hormone, itself capable of reducing the blood sugar level;
V. A combination effect of islet stimulation and direct action.

One must not assume that uniform effects upon the blood sugar level have been recorded by all who have studied the action of duodenal extracts. Mention has been made of the patently contradictory results, especially as to the initial effect upon the blood sugar level, from the injection of these extracts. Oehme and Wimmers [39] (1923) found that secretin depressed the blood sugar in rabbits during continuous intravenous glucose injections; but Troteano (1924) observed a mild hyperglycemia thirty minutes after the intravenous injection of secretin. Lambert and Hermann [30] (1925) saw both phenomena; a transitory hyperglycemia followed by a slight hypoglycemia. Fieschi [14] (1927) reported a slight hyperglycemia one-half hour after the injection, but at one and one-half hours he consistently observed a hypoglycemia. Hermann [21] (1926) stressed the transitory hyperglycemic effect; but Laughton and Macallum [32] (1932) could see neither a hypo- nor a hyperglycemic action from their duodenal preparation following its subcutaneous injections in rabbits.

While much confusion has resulted from these reports, most of the other workers observed the hypoglycemic action of the extracts. Among these are Penau and Simonnet [41] (1925), Takacs [52] (1927), and Heller [18, 19] (1929, 1931).

An adequate explanation for these conflicting reports is available in the literature. Although Hermann [21] did stress the transitory hyperglycemic phase resulting from the injection of secretin, he also noted that the injection of secretin free from the hypotensive factor failed to produce the temporary hyperglycemia and produced, instead, an initial hypoglycemia. By producing the hyperglycemic effect in a depancreatized dog, he showed that the hyperglycemic action of hypotensive secretin was not due to a temporary reduction of insular secretin. Using a dog with adrenal decapsulation, however, the hypotensive secretin failed to cause the usual transitory hyperglycemia, thus placing the responsibility for this action

upon a temporary increase of adrenalin. Goldstein,[17] somewhat later, obtained, with crude secretin, an increase in adrenalin concentration in the perfusion fluid of the isolated adrenal. Therefore, the observations of Hermann [21] and Goldstein [17] indicate that crude secretin contains a substance which is capable of increasing adrenalin secretion. In the work of Hermann [21] there is, too, direct evidence that the hyperglycemic effect of secretin is dependent upon the enhanced adrenalinemia. We think that there is sufficient evidence to attribute the increase in adrenalin to the histamine which must be present in crude secretin.

Although Parsons [40] did not consider the histamine amounts in the secretin preparations to be of physiological significance, the increase in blood sugar recorded by Chambers and Thompson [5] in canine histamine shock is so marked that the histamine in crude secretin might explain the mild and inconstant hyperglycemia observed. Especially congenial to such a concept is the report of La Barre,[23] who after suprarenal jugular anastomosis, saw a short and sudden augmentation of adrenalin in the blood of dogs after the injection, intravenously of histamine. In none of our cases (table 3) in whom we studied the effect of duodenal stimulation upon the fasting blood sugar, did we see any suggestion of a transitory hyperglycemia. Nor had such action been seen by any of the other investigators who had reported on duodenal stimulation in man.

With the reasonable certainty that extracts of duodenal mucosa were able to affect the blood sugar level, the nature of the agent and the *modus operandi* were studied.

## I. Is the Hypoglycemia Effect of Duodenal Extracts Due to Secretin?

Dixon and Wadia [10] did not believe it to be a secretin effect, because boiling the duodenal preparation with dilute acids destroyed the hypoglycemic effect but left the secretin action intact. This difference in the reactions of secretin and the hypoglycemic agent was further shown by Lalou [29] and Mellanby [36] in the rapid destruction of secretin by pepsin and trypsin, substances which are without effect upon the hypoglycemic agent. Heller [18] confirmed Mellanby [36] and then reported no decrease in the hypoglycemic activity of his product even after two hours' incubation with pepsin. He was unable to report uniform results with trypsin because the duodenal extract was affected by the alkalinity necessary for optimal tryptic activity.

Still and Shpiner [50] and Mellanby [36] on the one hand were unable to alter the blood sugar by the injection of purified secretin into normal or diabetic dogs, while Laughton et al.[31] could find no hormonal effect on the pancreatic secretion in dogs from their purified duodenal blood sugar reducing factor. Fresh acid preparations of duodenal mucosa produced an immediate and profuse flow of pancreatic juice. La Barre and Still [24] described a method

by which crude secretin can be separated into two fractions; one possesses very little secretagogic action, is non-hypotensive but highly hypoglycemic; the other is actively secretagogic and not at all hypotensive or hypoglycemic. They also showed that the incubation of crude secretin with pepsin-hydrochloric acid destroyed the secretagogic activity but did not affect the hypoglycemic action. It is evident, therefore, that the hypoglycemic factor which is extracted in the preparation of crude secretin, is separate and distinct from the secretagogic one.

## II. Is the Hypoglycemic Effect Due to an Extraction of Insulin from the Duodenum?

In 1924 Santos,[45] without presenting any confirmatory data, advanced the hypothesis that secretin very probably contained some substance such as insulin, which was responsible for its hypoglycemic action. In the same year Ivy and Fischer [22] obtained a product from the mucosa of hog duodenum and stomach by the Shaffer-Fischer procedure for preparing insulin which could produce hypoglycemia. They, too, seemed to feel that the product contained insulin which had been extracted from the intraduodenal insular tissue that exists in many animals. This opinion was confirmed by Mellanby [36] in 1928. There is, however, very definite evidence against such an explanation of the hypoglycemic action of duodenal extracts. In 1924, Epstein and Rosenthal mixed trypsin with insulin and injected the mixture after brief contact into fasting rabbits and so achieved an inactivation of the insulin. This inactivation occurred when the pH of the mixture was above 4.6, and was complete and remained permanent so long as the pH was above 4.8. Considering the hydrogen-ion concentration of the duodenum, the production of an active insulin in the duodenal lumen is a quite unexpected phenomenon.

Heller,[18] in 1929, using insulin-extracting methods on beef intestine, found no insulin in the upper small intestinal mucosa. La Barre and Still,[24] at about the same time, taking advantage of the fact that insulin is inactivated by pepsin-hydrochloric acid, showed the hypoglycemic action of crude secretin was not due to insulin because pepsin-hydrochloric acid failed to destroy its hypoglycemic action.

In view of the pepsin-hydrochloric action it is impossible to explain the effectiveness of the oral administration of intestinal preparations upon an insulin basis. Thus Heller [19] made extracts from rabbit and beef intestinal mucosa which, when given by mouth, were effective in lowering the blood sugar after intravenous glucose. This he confirmed in 1935 and found that in large enough dosage (five to ten times that used to reduce alimentary hyperglycemia) he could reduce even the normal blood sugar level. La Barre,[28] too, reported the oral effectiveness of his duodenal preparation in lowering blood sugar even in depancreatized dogs. Recently, Duncan, Shumway, Williams, and Fetter [12] using the Laughton-Macallum

extract orally were able to modify human diabetes. Further evidence that the hypoglycemic action is not due to an insulin extract from the duodenum has been supplied by Zunz and La Barre.[56] Using the method of pancreatico-jugular anastomosis between adrenal decapsulated dogs, they obtained a lowering of blood sugar after intravenous injection of non-hypotensive secretin in the donor that was much less marked than that in the recipient. This, of course, would not be expected to occur, if the extract were insulin.

Other differences in the action of the duodenal extracts as compared with insulin may be noted in the work of still other investigators. Thus, Takacs [52] reports that in many instances his duodenal extract produced a very conspicuous reduction of blood sugar (50 to 60 per cent) without the phenomena that go with insulin hypoglycemia. Such hypoglycemic phenomena did not appear even after the administration of very large doses of the extract. Duncan et al.,[12] too, recently remarked the fact that while they found their extract of value in reducing a marked hyperglycemia in human diabetics, they never saw any hypoglycemic reactions from the use of the extract. And Novao Santos [47] reports a case of a controlled diabetic in whom the injection of secretin produced, after two hours, a blood sugar of 38 mg. per 100 c.c., with no symptoms of a hypoglycemia. Takacs [52] also points out the much greater duration of the effect of his extract as compared with that of insulin. From this standpoint the observations of La Barre and Ledrut [27] and of La Barre [28] are also of interest. These investigators found that not only were they able to keep depancreatized dogs alive by the oral administration of their preparation, but also that they did not find it necessary to compensate for the absence of pancreatic ferments—a procedure which was indispensable in their treatment of a depancreatized animal with insulin.

## III. Is the Hypoglycemic Effect of Duodenal Extracts Due to Islet Stimulation?

In 1924, Troteano,[53] on the basis of experiments on dogs, concluded that the transitory hypoglycemic effect which follows the intravenous injection of secretin results from the stimulation of the insular apparatus of the pancreas. Many investigators since have supported this view. Dale [9] as far back as 1905 observed in both mammals and amphibia an increase in the number and volume of the islets of Langerhans after repeated injections of secretin. This work of Dale's was referred to in the report of Laughton and Macallum,[32] made a quarter-century later. These investigators found that animals receiving their duodenal preparation daily, over a period ranging from a week to 10 days, showed the effect on artificially induced hyperglycemia for two weeks following the last injection. This result they explain in terms of the islet-stimulation concept. Macallum [35] had previously postulated that diabetes might result from insular fatigue

occasioned by the excessive stimulation of the islets by the duodenal hormone. Freud and Saadi-Nazim [15] in 1926 further confirmed Troteano [53] by their results from the duodenal instillation of hydrochloric acid in dogs. In the same year, Dixon and Wadia [10] demonstrated the increase in pituitrin in the cerebrospinal fluid of dogs following the injection of duodenal extracts, a reaction which they believed to be of the same nature as that which followed injections of insulin. The following year Fieschi,[14] using secretin manufactured by the original Bayliss and Starling formula, noted that the sugar tolerance in dogs whose diet was rigorously controlled increased after prolonged treatment with secretin. Fieschi injected 10 c.c. three times a day for nearly 30 days. He noted that some of the animals which had a low tolerance at the beginning of treatment almost doubled their tolerance to ingested sugar by the end of the treatment. Usuelli [54] believed that the hyperemia of the pancreas which followed the injection of secretin, or the introduction of hydrochloric acid into the duodenum, determined the hyperactivity of both the external and insular secretory mechanism.

Gley and Hazard [16] from transfusion experiments following the duodenal instillation of hydrochloric acid concluded that the mechanism involved was islet stimulation. Finally, La Barre and Houssa [26] studied the effect of secretin produced in the duodenum upon a pancreas the exocrine portion of which had been destroyed. Injecting acid into the duodenum of a dog whose external pancreatic ducts had been ligated one to two months previously, and in which a bilateral suprarenalectomy had been performed just before the injection, these investigators saw a gradual hypoglycemia as marked in these animals as in those with an intact pancreas. They obtained a similar response even when the entire portion of the pancreas adhering to the duodenum was removed and the floating portion maintained as an abdominal subcutaneous graft.

The above cited investigations appear to indicate that the blood sugar reducing factor present in duodenal extracts operates through islet stimulation. To prove absolutely that this is the sole mode of action of the duodenal extract it would be necessary to show that it could not alter blood sugar without the aid of the pancreatic islet tissue. The obvious approach was the study of its action in the totally depancreatized animal.

## IV. Is the Hypoglycemic Action of Duodenal Extracts Due to a Separate Duodenal Hormone?

Oehme and Wimmers [39] in 1923 reported a hypoglycemic effect from secretin in four depancreatized dogs. The following year Ivy and Fischer [22] obtained an insulin-like substance from the duodenal mucosa with which they were able to reduce the blood sugar in a depancreatized dog. Penau and Simonnet [41, 42] reported similarly. Takacs [52] found his duodenal preparation effective in depancreatized animals when administered intravenously, subcutaneously, orally or by rectum. La Barre and Still [24] also reported

the efficacy of crude secretin in lowering the blood sugar of totally diabetic dogs, and La Barre and Ledrut [27] were able to obtain through the hydrolysis of secretin, a non-secretagogic fraction which was especially effective in reducing the blood sugar of depancreatized animals. Other observers such as Novao Santos,[45, 46] Criado,[8] Laughton, Macallum, Rabinowitch and Watson,[31] and Laughton and Macallum [32] were unable to influence the blood sugar of depancreatized animals with their duodenal extracts. In such investigations, however, positive findings, if repeated, are more significant than negative results.

## V. Is the Hypoglycemic Action of Duodenal Extracts a Combination of Islet Stimulation and Direct Action?

While the results obtained by certain investigators in the depancreatized animals indicate that the duodenal extracts are capable, alone, of reducing the blood sugar, there is some evidence that in the intact animal they enhance islet activity as well. Zunz and La Barre [57] have shown that secretin can increase the output of insulin. Using adrenalectomized dogs with pancreatico-jugular anastomoses, they found that purified secretin injected into the donor dog caused a drop in blood sugar in both the donor and recipient, with the fall more marked in the latter. Since in this experiment, the donor is physiologically depancreatized, the above results may be interpreted as a double action of the secretin. This concept is fortified by their findings with jugulo-jugular anastomoses; the injection of secretin into the donor produced only a slight decline in the recipient which was less marked than that which occurred in the donor. La Barre and Still reported confirmation of some of these experiments.

Additional suggestive data for the dual action are to be found in the results of Takacs.[52] He noted that depression of the blood sugar following the administration of the duodenal preparation lasted a much shorter time in the depancreatized animal than in the intact one. Clinically, too, both Laughton et al.[31] and Duncan and his associates [12] report their best results with the Laughton-Macallum extract in the milder cases of diabetes.

Our experiments in human beings offer data which do not seem to confirm exactly the probable mechanism as observed in lower animals. It is, of course, impossible to duplicate in man the experimental conditions of animals which permit a study of the effect on the blood sugar of duodenal stimulation in the absence of the pancreas. The closest simulation to such conditions probably was obtained in our case in chart 7. Unfortunately, this man who appeared to have a diffuse calcification of the pancreas was available for only a few studies. It would appear from comparison of chart 7 with the remaining charts that, in man, by far the major effect on the blood sugar of duodenal stimulation is due to islet stimulation rather than to the direct action of a duodenal hormone. This is supported by the greater efficacy of duodenal extracts in the milder cases of clinical diabetes.

## The Relationship of the Hypoglycemic Duodenal Factor to the Autonomic Nervous System

Despite the studies of Zunz and La Barre [57] which showed that vagotomy does not prevent the action of the sugar reducing factor in injected duodenal extracts, it would appear from the work of Heller [20] that some of this action

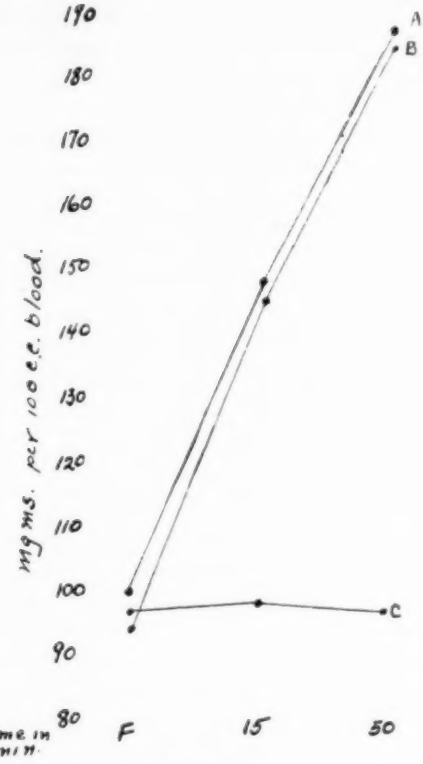


CHART 1

Curve *A* = Blood sugar readings (*F*) fasting and at 15 and 30 min. after the ingestion of 225 c.c. of 38.4% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min. = 25.5 gm.

Curve *B* = Blood sugar readings (*F*) fasting and at 15 and 30 min. after the duodenal instillation of 20 gm. of glucose in isotonic solution.

Curve *C* = Blood sugar readings (*F*) fasting and at 15 and 30 min. after the ingestion of 225 c.c. of 41.5% glucose and simultaneous duodenal instillation of 0.47% HCl at 100 gtts. per min. Total glucose lost from stomach in 30 min. = 20.6 gm.

was dependent upon intact vagi. This investigator found, by chemical elimination of the vagus by atropine and of the sympathetics by ergotamine, that while the action of the intestinal extract was retained, its effect was reduced.

Whether the duodenal extracts are able to influence adrenalin hyperglycemia is not quite clear. Laughton and Macallum [32] report a marked lowering of the level of adrenalin hyperglycemia in rabbits and dogs by

injection of their duodenal extract. Heller [20] saw an effect from his extracts under similar conditions, but not a very distinct one.

We are not familiar with any previous studies on man of the influence of direct duodenal stimulation on hyperglycemia so produced. We studied this effect in 10 patients. After intubation of the duodenum of a fasting subject we injected 10 minims of adrenalin chloride (1–1000) subcutan-

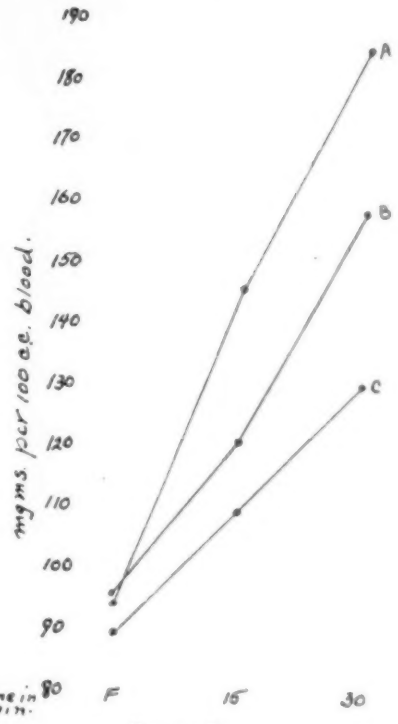


CHART 2

Curve $A$ = Blood sugar readings ($F$) fasting and at 15 and 30 min. after the duodenal instillation of 25 gm. of glucose in isotonic solution.

Curve $B$ = Blood sugar readings ($F$) fasting and at 15 and 30 min. after the duodenal instillation of 62.5 c.c. of 40% glucose (25 gm.).

Curve $C$ = Blood sugar readings ($F$) fasting and at 15 and 30 min. after the duodenal instillation of 500 c.c. of 5% glucose (25 gm.) in 0.3% HCl.

eously, having previously taken blood for sugar determination. Blood samples were taken at 15 minute intervals for one hour during which nothing was instilled into the duodenum. On a subsequent day the same procedure was repeated, except that, in addition, the duodenal instillation of 0.4 per cent hydrochloric acid at the rate of 60 to 80 drops per minute was started simultaneously with the injection of the adrenalin, and was continued throughout the hour of the test period. On still another day the duodenal instillation of the acid was started 15 minutes before the injection of the adrenalin. Charts 8 and 9 illustrate the results obtained, the former in a patient with a normal gastric secretion, the latter in a case of anacidity.

In chart 8, we note that the subcutaneous injection of 10 minims of adrenalin chloride (1–1000) after an overnight fast produced a change in glycemia from 98 mg. to 178 mg. per 100 c.c. in the course of an hour, a rise of 85 mg. Under similar conditions of adrenalin action, the simultaneous instillation of 0.5 per cent hydrochloric acid at the rate of 60 drops per minute during the course of the hour, resulted in a change in blood sugar concentration from a fasting level of 87 mg. to 186 mg. per 100 c.c., a rise

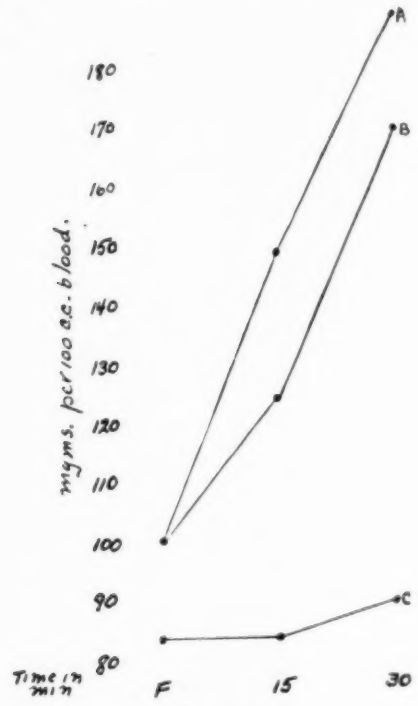


CHART 3

Curve *A* = Blood sugar readings (*F*) fasting and 15 and 30 min. after the ingestion of 225 c.c. of 38.4% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min. = 25.5 gm.

Curve *B* = Duodenal instillation of 0.47% HCl at 100 drops per min. for 15 min. Acid stopped. Then duodenal instillation of 500 c.c. of 5% glucose (rapidly). Blood sugar (*F*) fasting at 15 and 30 min. after the instillation of the glucose (25 gm.).

Curve *C* = Duodenal instillation of 0.47% HCl at 100 drops per min. for 15 min. Acid stopped. Then duodenal instillation of 50 c.c. of 50% glucose. Blood sugar (*F*) fasting and at 15 and 30 min. after the instillation of the glucose (25 gm.).

of 99 mg. per 100 c.c. of blood. Starting the duodenal instillation of the acid 15 minutes before the injection of the adrenalin did not alter the result. The changes in chart 9 parallel those recorded in chart 8. Similar results were obtained in all of the 10 cases studied. It is, therefore, evident that duodenal stimulation in man is not capable of modifying adrenalin hyperglycemia.

## The Effect of Duodenal Stimulants Other Than Hydrochloric Acid in the Prevention of Alimentary Hyperglycemia

Bayliss and Starling [1] at first believed that the action of the hydrochloric acid was essential to the extraction of active secretin from the mucosa. It was soon learned, however, that many agents, such as soap, chloral hydrate, sodium chloride, sugar, alcohol, acetone and others, could extract an active secretin under similar conditions.

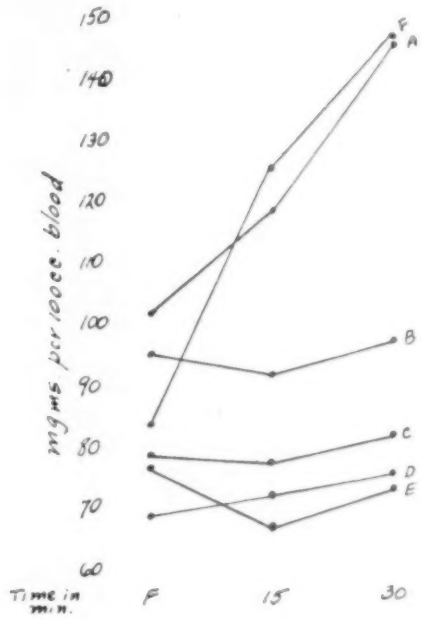


Chart 4

Curve *A* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the ingestion of 225 c.c. of 40.8% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min. = 26.4 gm.

Curves *B*, *C*, *D* and *E* = Blood sugar readings fasting (*F*) and 15 and 30 min. after the ingestion of 225 c.c. of 40% glucose and simultaneous duodenal instillation of 0.45% HCl at 60, 70, 80 and 100 drops per min. respectively. Total glucose lost from stomach in 30 min. = 19.9, 18.2, 20.9 and 23 gm. respectively.

Curve *F* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the duodenal instillation of 23 gm. of glucose in isotonic solution.

We [48] have shown, too, that the intrinsic agent which activates the local duodenal mechanism concerned in the motor activity of the stomach and pylorus, is the gastric hydrochloric acid. It was also pointed out that other substances added in food, which were through chemical or physical action capable of stimulating the duodenal mucosa, could also effect pyloric closure. The present studies were, therefore, extended along these lines and the action of fats, isotonic and hypertonic solutions of sodium bicarbonate and sodium chloride, as well as hypertonic solutions of glucose were investigated. Chart 5 illustrates the effects produced by these various

substances instilled into the duodenum while glucose is being absorbed from the stomach. With oil, hypertonic bicarbonate or hypertonic saline solutions, effects are seen which are identical with those obtained from the duodenal instillation of hydrochloric acid. They consist, as before, of no appreciable rise in blood sugar during the period of duodenal instillation even though quantities of glucose are being absorbed from the stomach which would ordinarily cause a sharp rise in blood sugar. (Curve 4, chart 5.) Chart 6 illustrates a similar action of fat in our diabetic patient.

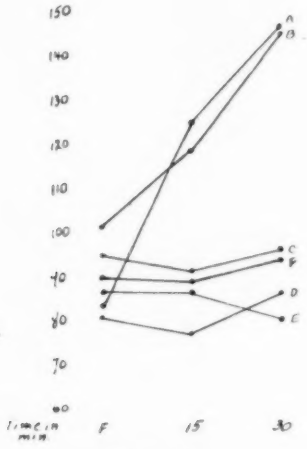


CHART 5

Curve A = Blood sugar readings fasting ($F$) and at 15 and 30 min. after the duodenal instillation of 23 gm. of glucose in isotonic solution.

Curve $B$ = Blood sugar readings fasting ($F$) and at 15 and 30 min. after the ingestion of 225 c.c. of 40.8% glucose. No duodenal instillation. Total glucose lost from stomach in 30 min. = 26.4 gm.

Curve $C$ = Blood sugar readings fasting ($F$) and at 15 and 30 min. after the ingestion of 225 c.c. of 40% glucose and simultaneous duodenal instillation of 0.45% HCl at 60 gtts. per min. Total glucose lost from stomach in 30 min. = 19.9 gm.

Curve $D$ = Blood sugar readings fasting ($F$) and at 15 and 30 min. after the ingestion of 225 c.c. of 41.0% glucose and simultaneous duodenal instillation of 5% NaCl at 80 gtts. per min. Total glucose lost from stomach in 30 min. = 21 gm.

Curve $E$ = Blood sugar readings fasting ($F$) and at 15 and 30 min. after the ingestion of 225 c.c. of 40.5% glucose and simultaneous duodenal instillation of olive oil 80 gtts. per min. Total glucose lost from stomach in 30 min. = 20.2 gm.

Curve $F$ = Blood sugar readings fasting ($F$) and at 15 and 30 min. after the ingestion of 225 c.c. of 39.8% glucose and simultaneous duodenal instillation of sod. bicarb. (7%) 60 gtts. per min. Total glucose lost from stomach in 30 min. = 24.2 gm.

Charts 2 and 3 indicate that glucose itself in hypertonic solution in the duodenum calls forth the same mechanism as do other agents. Thus in chart 2, one sees after the duodenal instillation of 25 grams of glucose in isotonic solution a rise in blood sugar from a fasting level of 93 mg. to 185 mg. in a half hour, a rise of 92 mg. of glucose per 100 c.c. of blood (curve A). When the same amount of glucose in hypertonic solution (40 per cent) is instilled into the duodenum on another day the change in blood sugar concentration in the following half hour is distinctly less marked.

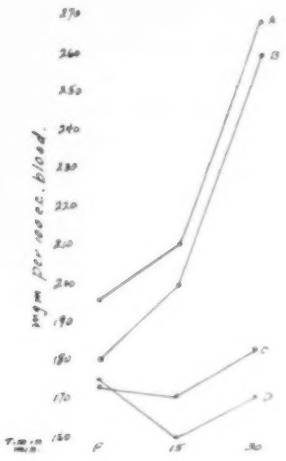


CHART 6

Curve *A* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the ingestion of 225 c.c. of 38.5% glucose. No duodenal instillation. Total glucose lost from stomach 38.6 gm. in 30 min.

Curve *B* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the duodenal instillation of 25 gm. of glucose in isotonic solution.

Curve *C* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the ingestion of 225 c.c. of 41.7% glucose and simultaneous duodenal instillation of olive oil 60 gtts. per min. Total glucose lost from stomach in 30 min. = 18.5 gm.

Curve *D* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the ingestion of 225 c.c. of 40.0% glucose and simultaneous duodenal instillation of 0.47% HCl at 80 gtts. per min. Total glucose lost from stomach in 30 min. = 31.5 gm.

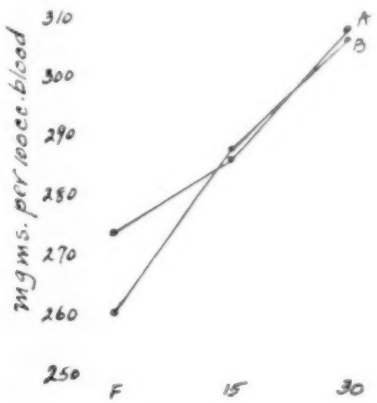


CHART 7

Curve *A* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the ingestion of 225 c.c. of 41.7% glucose and simultaneous duodenal instillation of 0.47% HCl at 80 gtts. per min. Total glucose lost from stomach in 30 min. = 27.6 gm.

Curve *B* = Blood sugar readings fasting (*F*) and at 15 and 30 min. after the duodenal instillation of 25 gm. of glucose in isotonic solution.

Thus the rise was from 96 mg. to 158 mg., a change of 62 mg. per 100 c.c. of blood (curve B). One sees also in this chart (curve C) how much greater is the stimulating action of 0.3 per cent hydrochloric acid. When the 25 grams of glucose in isotonic concentration are made up in 0.3 per cent hydrochloric acid and instilled into the duodenum, the subsequent change in blood sugar is the least in this group of experiments, a change this time from a fasting level of 88 mg. to 129 mg., a rise of only 41 mg. of glucose per 100 c.c. of blood.

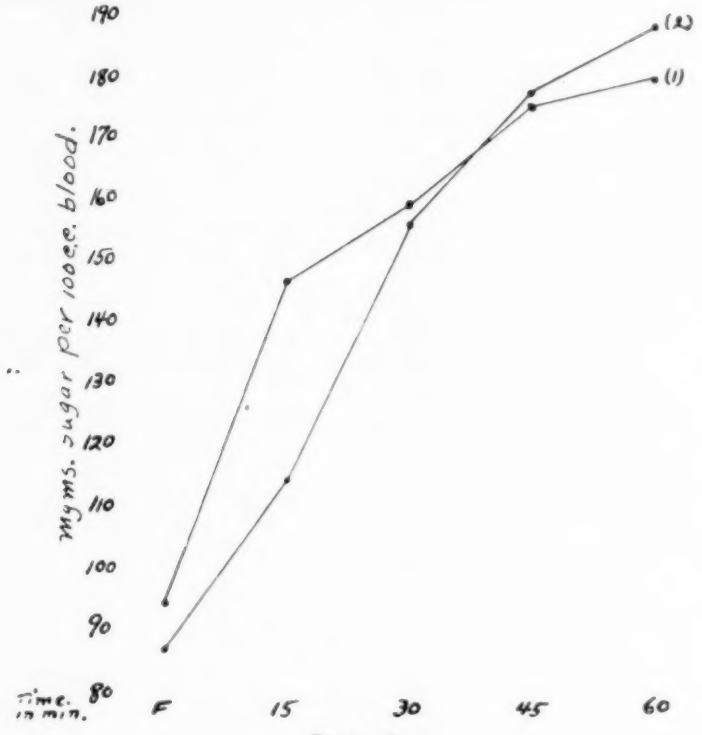


CHART 8

Normal gastric acidity. (1) Blood sugar curve after 10 min. of adrenalin chloride (1–1000) subcut. (2) Same as (1) plus 0.51% HCl intraduodenally 60 gtts. per min.

Chart 3 also strikingly illustrates the difference in action of relatively isotonic glucose and markedly hypertonic solutions. Thus for curve B, 0.47 per cent hydrochloric acid was instilled into the duodenum at the rate of 100 drops per minute, for 15 minutes. The acid was then stopped and 500 c.c. of 5 per cent glucose rapidly instilled into the duodenum. The blood sugar before the instillation of the glucose was 100 mg. per 100 c.c. One-half hour after the glucose the blood sugar had risen to 169 mg., a change of 69 mg. per 100 c.c. of blood. The experiment repeated (curve C) with the exception that the 25 grams of glucose were now instilled into the duodenum in a 50 per cent solution, produced a change in blood sugar

concentration in the following half hour of only 6 mg. per 100 c.c. of blood. Chart 3 also indicates that the hypoglycemic action resulting from duodenal stimulation is probably effective only so long as the duodenal stimulant is applied to the mucosa, or at least not after the stimulation is adequately diffused or diluted. Curve A in chart 3 was obtained in the half hour after the ingestion of 225 c.c. of 38.4 per cent glucose. At the end of the half hour an analysis of the recovered gastric contents indicated that 25.5 grams of glucose had either been absorbed or had entered the duodenum. The blood sugar concentration changed from a fasting level of 100 mg. per 100 c.c. to 188 mg., a rise of 88 mg. per 100 c.c. In curve B we find that the

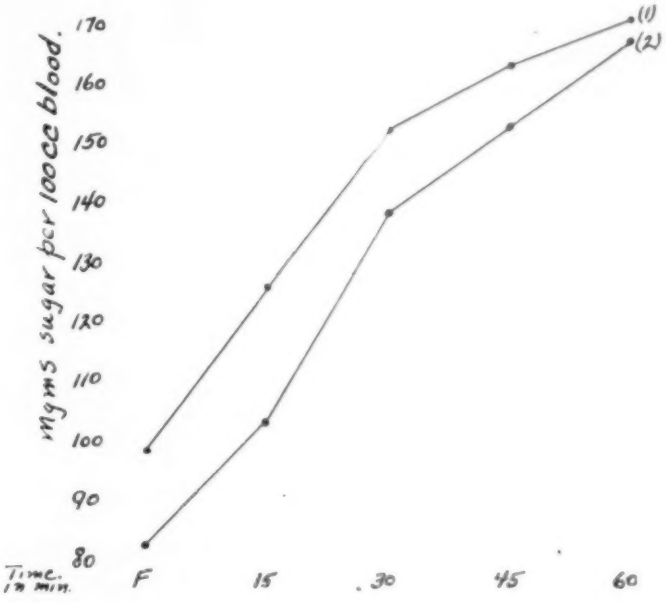


CHART 9

Gastric anacidity (1) Blood sugar curve after 10 min. of adrenalin chloride (1–1000) subcut. (2) Same as (1) plus 0.51% HCl intraduodenally 60 gtts. per min.

preceding instillation of 0.47 per cent hydrochloric acid had little effect upon the rise of the blood sugar level following the duodenal instillation of 500 c.c. of 5 per cent glucose, a total amount of glucose comparable to that which had been utilized previously. This is significant when compared with the results recorded for example in chart 1, where the hydrochloric acid action upon the duodenal mucosa was maintained during the period of glucose absorption. In curve B of chart 3, the stimulating effect of the hydrochloric acid upon the duodenal mucosa was rapidly diluted by the introduction of a large amount of relatively isotonic glucose, which in itself has no local stimulating action. Curve C, chart 3, on the other hand, shows a sharply contrasting result even though the same total quantities of

hydrochloric acid and glucose were used. In this instance, however, the stimulating mucosal effect of the hydrochloric acid instead of being dissipated, is if anything, enhanced by the markedly hypertonic glucose solution. We see, therefore, in curve C, a result as definite as if continued duodenal stimulation had been maintained.

## Summary

A brief historical survey is furnished of the development of our knowledge of the results of duodenal stimulation beginning in 1825 when Leuret and Lassaigne observed the pancreatic effect of acid applied to the ampulla of Vater in the horse and dog. Various steps led up to the discovery of secretin by Bayliss and Starling. Duodenal extracts were later shown to contain separable hypoglycemic and secretagogic agents. The literature dealing with the nature and mode of action of the hypoglycemic agent is critically analyzed.

Our method for studying this duodenal hypoglycemic mechanism in man derives from earlier studies of the gastric absorption of concentrated glucose solutions. A method is described whereby the effect of duodenal stimulation upon the utilization of the glucose absorbed from the stomach may be determined. The method of determining the effect of such stimulation upon adrenalin hyperglycemia is likewise described.

The data from our own studies appear to indicate the following:

1. Glucose, at least when in high concentration, may be absorbed by the human stomach.

2. Duodenal stimulation by hydrochloric acid will prevent a rise in blood sugar even though the amounts of sugar absorbed from the stomach would ordinarily raise the blood sugar level.

3. The same effect was observed in one diabetic patient but did not occur in another very severe diabetic with a calcified pancreas.

4. The prevention or counteraction of alimentary hyperglycemia by duodenal stimulation is shown to be not a function solely of hydrochloric acid. Other agents which could stimulate the duodenal mucosa were equally efficacious. Thus similar results were obtained with fat, hypertonic solutions of sodium chloride and sodium bicarbonate, and of glucose itself.

5. While duodenal stimulation could prevent alimentary hyperglycemia, peculiarly enough, it did not carry the depression of glucose concentration below the fasting level. These observations are similar to those of Laughton and Macallum who found that their duodenal extract did not reduce the blood sugar below the normal resting level after induced hyperglycemia.

6. Duodenal stimulation did not alter the normal fasting blood sugar level.

7. Duodenal stimulation failed to prevent or decrease the hyperglycemia incident to adrenalin chloride injection.

From a study of the literature on the effect of duodenal extracts and their possible method of action, we believe there is adequate evidence to show that their action is not due to secretin or to an insulin extract from the duodenum. It would appear to depend, in the dog, upon a combination of islet stimulation and direct action of a duodenal hormone upon glucose metabolism. From the results reported in the depancreatized animal, the direct action is the essential one. From our data in a severe diabetic, it would seem that, in man, the duodenal mechanism is essentially concerned with islet stimulation. It would seem, therefore, that little could be expected from the use of duodenal extracts in the treatment of diabetes in man. In the mild cases of diabetes there may be some effect from islet stimulation; in severe diabetes there is probably no effect or even an injurious one by stimulation of already severely damaged islets.

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# CHRONIC HYPOCHROMIC ANEMIA IN WOMEN

## ITS GASTROINTESTINAL, GYNECOLOGIC, ENDOCRINE AND PSYCHIATRIC FEATURES*

By Solomon G. Meyers, M.D., A. Hazen Price, M.D., F.A.C.P., H. C. Mack, M.D., Linus J. Foster, M.D., and E. A. Sharp, M.D., F.A.C.P., *Detroit, Michigan*

So-called *idiopathic hypochromic anemia* has been frequently discussed in the literature. Most authors emphasize the hematological aspects, neglecting other important clinical features presented by patients with hypochromic anemia which seem to us to have an important etiologic bearing. Moreover, failure to take proper cognizance of these conditions in our opinion precludes the possibility of intelligent management. These conclusions are the result of studies which will be reported below. In our opinion, the term *idiopathic* as applied to hypochromic anemia is seldom justified.

The present report is based on an intensive study of 26 women with chronic hypochromic anemia, special emphasis being placed on the gastrointestinal, endocrine, gynecologic and psychiatric problems which these patients presented. Our approach to the problem along these lines was prompted by the frequent presenting complaints of "nervousness" and "indigestion" which are also emphasized in the literature in describing this condition. Our aim was to determine possible organic or functional backgrounds for these symptoms. Gynecologic surveys were, of course, imperative since our series was composed exclusively of women. Endocrine investigations were indicated by the surprising frequency with which symptoms of glandular dysfunction were encountered. Neuro-psychiatric examinations were undertaken to determine the significance of "nervous" complaints. As a group, these patients showed a striking uniformity as to symptoms, blood findings, as well as clinical behavior before and after therapy.

*Nationality and Race.* This group represents various Caucasian nationalities. Jewish patients, although comprising 3.4 per cent of the Harper Hospital Out-Patient Department attendance, are not represented in this series. Curiously enough, also, there were no negroes, although 7.2 per cent of the clinic enrollment is colored. Conclusions as to a racial predisposition are, of course, not suggested from this small series.

*Social and Economic Factors.* All patients of this series represent the low-income class characteristic of dispensary practice during "depression" times.

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*Age.* The youngest patient in this series was 22 years of age, the oldest 48 years. The average age was 38 years.

*Period of Observation.* Average: 27.3 months.

## Hematologic Features

The hematologic features of the 26 patients studied are summarized in table 1. It is worthy of note that seven, or 30 per cent, of these patients showed a macrocytosis upon admission. This morphologic characteristic is found in anemia of long duration, and is also a frequent indication of blood regeneration due to postpartum bleeding, uterine hemorrhage from fibroids, functional uterine bleeding and multiple pregnancy.

TABLE I

Hematologic Features

| | | | |
|---|---|---|---|
| *On admission* | | | |
| Average hgb. | 51% | Range | 33%–69% |
| Erythrocyte count | 3,600,000 | Range | 2 million to 4.5 million |
| Average color index | 0.7 | | |
| Mean diameter of red blood cells—7.7 or over | | | 7 cases—30% |
| Mean diameter of red blood cells—7.4 to 7.6 | | | 8 cases—35% |
| Mean diameter of red blood cells—7.3 or below | | | 8 cases—35% |
| Average leukocyte count | 6,200 | Range | 3,250 to 11,000 |
| *After treatment* | | | |
| Average hgb. | 92.8% | Range | 65%–110% |
| Erythrocyte count | 4,660,000 | Range | 3.5 million to 5.5 million |
| Average color index | 1.0 | | |
| Good hematologic response and good clinical response | | | 12 cases—46% |
| Good hematologic response and fair clinical response | | | 5 cases—19% |
| Good hematologic response and poor clinical response | | | 8 cases—31% |
| Poor hematologic response and poor clinical response | | | 1 case — 4% |

In the remaining 16 patients, normocytic and microcytic diameters occurred an equal number of times. Three of the patients showing microcytosis were sisters. All had a typical picture of idiopathic achlorhydric anemia. The appellation *idiopathic* applied to the three cases in question or to others in the microcytic group, is hardly justified since disease entities believed to be exciting or contributory causes of the anemic state were associated.

Hemopoietic improvement and favorable alteration in the patient's general physical condition were by no means parallel. While anti-anemic therapy was uniformly effective, a multiplicity of general complaints persisted during and after hemopoietic recovery. When both blood count and general condition responded favorably, iron alone was usually sufficient to cause remission of symptoms, although in a few cases liver or ventriculin was found to be helpful. On the other hand, poor or fair clinical results were not due to persistence of the anemia since little difficulty was encountered in restoring blood balance in these cases. The group, therefore,

showing indifferent general response created the impression that factors other than anemia were present. Among the most frequently associated conditions retarding full recovery were gastrointestinal disorders, endocrinopathies (particularly thyroid deficiency and entities causing excessive menstruation), and nervous system instability. In order to meet the individual therapeutic requirements of this series of patients, it is obvious that a rather comprehensive regimen had to be adopted. Among the hormones, desiccated thyroid, parathyroid extract, Antuitrin-S, Theelin and Pituitrin were employed; dietary adjustment, hydrochloric acid, laxatives and sedatives were necessary to control the gastrointestinal complaints; while snake venom, calcium, dilatation and curettage, and induction of menopause by radiation or surgical procedures were used in an effort to control the gynecologic conditions. Social adjustment was encouraged by appropriate psychotherapeutic methods.

It is evident that anemia is an expression of disease and seldom exists as a solitary clinical entity. It is equally obvious, then, that its corrective measures cannot be restricted to any one specific group of medicament. Numerous therapeutic endeavors are required in the comprehensive management of the anemic patient. Hence in planning treatment, this concept should govern the hematologist and clinician.

## Gastrointestinal Features

Atrophy of the lingual papillae with the production of a smooth tongue was present in 25 per cent of our cases. An additional 12 per cent complained of burning of the tongue in the absence of atrophy.

The gastric acidity was determined one or more times in each case (see table 2). True achylia, with no response to alcohol ingestion or histamine injection, was present in 54 per cent; false achylia (no free acid after alcohol meal, but present after histamine injection) in 12 per cent; and hypoacidity (free acid 0 to 20) in 15 per cent. Acidity was less than normal, therefore, in 81 per cent of our cases. The crucial rôle which free hydrochloric acid plays in the digestion and utilization of blood building elements from food has been pointed out by Mettier, Kellogg and Rhinehart.[1]

Gastrointestinal symptoms have been repeatedly described in this disease, usually being referred to as "indigestion" or "dyspepsia." An attempt was made to analyze more exactly the nature of the dyspepsia by the use of clinical and roentgenologic methods. Table 2 reveals the gastrointestinal diagnoses made in our series. Seventy-three per cent of the patients had disturbances of colonic function of the type usually referred to as unstable colon (Kantor [2]) or irritable colon (Jordan and Kiefer [3]). This condition is marked by pain in any portion of the abdomen, never severe but present over long periods of time, and often accompanied by belching, a

sensation of distention, constipation, diarrhea, or alternating constipation and diarrhea.

The digestive symptoms were often the outstanding ones, overshadowing the evidence of anemia. Treatment which raised the blood levels to normal did not as a rule alleviate the dyspepsia. The digestive disorder may also be a cause for failure of treatment or for immediate recurrence of anemia since these patients often choose a bland diet, high in starches and low in meats, vitamins and iron containing vegetables. The caloric intake may also be low because of the distress occasioned by food; and the cathartics frequently taken may interfere with absorption.

TABLE II

Digestive Symptoms

| | | |
|---|---|---|
| *A.* | Tongue smooth | 25% |
| | Tongue not atrophic but complains of burning | 12% |
| | Tongue not atrophic | 63% |
| *B.* | Gastric acidity: | |
| | True achylia | 54% |
| | (No free acid after alcohol or histamine) | |
| | Pseudo achylia | 12% |
| | (No free acid after alcohol, free acid present on histamine injection) | |
| | Hypoacidity | 15% |
| | (Free acid after alcohol 0° to 20°) | |
| | Normal acidity (20° to 40°) | 15% |
| | Hyperacidity (40° and over) | 4% |
| *C.* | Gastrointestinal diagnoses: | |
| | Irritable colon | 19 cases, (73%) |
| | Constipation, no subjective symptoms | 2 cases |
| | Internal hemorrhoids | 4 cases |
| | Probable cholecystitis | 3 cases |
| | Chronic appendicitis | 1 case |
| | Oxyuris infestation | 1 case |
| | Indigestion, unclassified | 1 case |
| | No gastrointestinal symptoms | 3 cases |

In addition to colonic disturbances, other gastrointestinal conditions were also present, such as internal hemorrhoids, cholecystitis and oxyuris infestation. Only three patients (12 per cent) did not complain of gastrointestinal symptoms.

Because of the frequent occurrence of irritable colon, our patients were routinely given a diet high in meat and green vegetables, in which the gas producing foods as cabbage, cucumbers, raw apple, fried and spicy foods were eliminated (see anti-anemic diet). Other agents were frequently employed: anti-spasmodics (belladonna), sedatives (bromide or phenobarbital), and mineral oil by mouth, or olive oil by retention enema. The gastrointestinal symptoms were quite satisfactorily controlled by this type of management.

All patients with deficient gastric acidity were given dilute hydrochloric acid. Occasionally a case was noted where the dyspepsia disappeared immediately after the addition of acid therapy.

Following the suggestion of Gray and Wintrobe,[4] a dietetic history was taken to reveal the food intake during the development of the anemia. The following dietary abnormalities were noted:

| | |
|---|---|
| Low meat and iron intake | 32% |
| Low calcium intake | 49% |
| Low vitamin A | 4% |
| Low vitamin B and C | 36% |
| High starch intake | 44% |

These figures are not surprising when one considers that we are dealing here with clinic patients in depression years.

In general, patients on a low meat diet also ate other foods low in iron. About half the patients had a low calcium intake, a situation not peculiar to anemic patients since it has been shown that adults generally have a negative calcium balance, the patients drawing on the reserves of these substances stored in bone.

The low fruit and vegetable intake caused not only a deficiency of iron but also of vitamins B and C. The high starch diet taken by 44 per cent of the patients is common in the average American dietary.

The diet list routinely given to our patients was designed to increase the meat and iron intake, and to provide adequate minerals, vitamins and calories.

## Endocrine Features

(*a*) *Thyroid Function:* Thyroid function was determined by clinical signs and symptoms, determination of the basal metabolic rate and by response to thyroid therapy. Results of the survey showed:

| | | |
|---|---|---|
| Normal thyroid function | 12 cases, | 48% |
| Hypothyroidism | 12 cases, | 48% |
| Low metabolic rate without hypothyroidism | 1 case, | 4% |
| (no data, 1 case) | | |

Hypothyroidism was present in about one-half of our patients and was moderate in degree, there being no cases of myxedema. Two patients with hypothyroidism had had previous thyroidectomies. In many, the hypothyroidism would have remained undiscovered unless looked for specifically. Basal metabolic rates were only of corroboratory value, seven of the 12 having rates from 0 to — 10, and five from — 11 to — 20; none were below — 20. A single case had a low basal rate (— 17 per cent) without clinical hypothyroidism; her condition became worse on the administration of thyroid extract.

Anemia accompanying myxedema is well known and will often respond to thyroid extract where iron therapy is unsuccessful. It is our opinion that minor degrees of hypothyroidism play some rôle in the production of anemia, perhaps because the rate of iron metabolism is diminished.

Patients with anemia frequently manifest symptoms bearing a marked resemblance to those of hypothyroidism, namely fatigue, dry skin, brittle nails, and abnormal sensitivity to cold weather. A further resemblance is that the basal metabolic rate is said to be lowered in anemia. The clinical survey of the patient for evidences of hypothyroidism was made after the anemia had been wholly or largely corrected by anti-anemic therapy; metabolic rate determinations were again made when the blood had reached a normal or almost normal level. Another criterion for the diagnosis of hypothyroidism was a favorable response to thyroid medication. Demonstration of hypothyroidism was important since clinical improvement resulted from the administration of thyroid extract in patients who were persistently fatigued even after the blood level had been brought back to normal.

### Obstetrical and Gynecological Factors

(*a*) *Menstrual Function:* Of the 26 patients, 17 (65 per cent) gave a history of marked menorrhagia. Two (8 per cent) had moderate menorrhagia, and the remaining seven (27 per cent) had menstruated normally. Eight patients had reached or were approaching the menopause; two had artificial menopause induced by us because of excessive vaginal bleeding, one by irradiation, one by surgical measures.

Of the 19 who menstruated profusely, 10 (55 per cent) had normal thyroid function, and 9 (45 per cent) had signs and symptoms of hypothyroidism. It is generally believed that menorrhagia is more commonly associated with hypothyroidism than with hyperthyroidism. One of our patients, however, complained of menorrhagia while hyperthyroidism was present; when hypothyroidism developed after her fourth thyroid operation, menorrhagia persisted to such a degree that artificial menopause was induced by irradiation.

(*b*) *Multiple Pregnancy:* The factor of multiple pregnancy was present in five cases; four patients had had 10 or more pregnancies; and one patient had had six pregnancies within six years.

Pregnancy not only is an important etiologic factor in the anemia but also an important one in causing relapse of anemia in patients who are under control. One patient who had borne eight children before coming under our care had her blood levels brought up to normal, only to relapse in each of the two subsequent pregnancies.

(*c*) *Gynecological Factors:* No organic causes for vaginal bleeding could be demonstrated in the entire group. Five (18 per cent) were subjected to dilatation and curettage to rule out the organic causes for the bleeding. The whole group presented the usual run of minor gynecological pathology such as endocervicitis, trichomonas vaginalis vaginitis, cystocele, atrophic vaginitis. None of these were thought to have any bearing on the vaginal bleeding or anemia.

Other types of endocrine therapy, aside from thyroid extract, were used in nine cases. Theelin was administered to five patients to counteract meno-

pausal symptoms. Antuitrin-S was given to two patients to diminish the menstrual flow. In one case the periods became more regular, though without diminution in the quantity of blood lost. In another, 55 injections of Antuitrin-S (averaging 2 c.c. per injection) were given. In addition, she received Theelin, Pitocin, surgical Pituitrin, parathyroid extract, and injections of snake venom, all without effect on the menorrhagia. Curettage showed a normal premenstrual endometrium. We are considering temporary roentgen-ray castration. In several of our patients the menstrual flow became normal after the administration of iron alone.

## Neuro-Psychiatric Features

Previous writers have characterized patients with hypochromic anemia as suffering from nervousness, fatigue, and a worrisome disposition. In an attempt to classify this nervousness more exactly, our patients received a neuro-psychiatric survey.

None of our patients showed objective neurological findings. This is in great contrast to our cases of treated pernicious anemia who had many neurological findings though few somatic complaints. In the hypochromic group there was a multiplicity of complaints of a widely varying nature.

Table III

Psychiatric Status

| | |
|---|---|
| (*a*) No nervous complaints | 5 cases |
| (*b*) Complaints proportionate to physical ailments | 3 cases |
| (*c*) Mild anxiety state | 2 cases |
| (*d*) Anxiety neurosis | 4 cases |
| (*e*) Asthenia, hypochondriac type | 2 cases |
| Total with normal personality | 16 cases or 64% |
| Constitutional psychopathic inferiority | 6 cases or 24% |
| Psychasthenia | 1 case or 4% |
| Menopausal psychosis | 1 case or 4% |
| Manic depressive psychosis | 1 case or 4% |
| (No psychiatric survey, 1 case) | |

Table 3 shows the status of 25 patients who received psychiatric study. This shows that one-fourth of the patients fall into the class of *constitutional psychopathic inferiority.* Such persons have difficulty in adjusting themselves to the ordinary problems of life. Their inability to adjust results in fixation upon numerous minor physical complaints to which the average individual would give no audience. Of the six patients classified as *constitutional psychopathic inferiors,* four were of the hypochrondriac type with mental depression and centering of maladjustment on somatic complaints; the remaining two were of the inadequate personality type, with inability to adjust to the ordinary rigors of life and resorting to fixation on somatic complaints as an escape from reality. These patients were particularly difficult to treat because they lack insight into their problems.

In the group classified as having a normal mentality, there were only five (20 per cent) who had no nervous complaints; three (12 per cent) had nervous complaints which were justified by their physical ailments. The remaining eight cases (32 per cent) with normal personalities had encountered domestic and financial situations during the period of treatment that caused emotional states of the anxiety type.

There were two cases of true psychosis, one of menopausal psychosis with paranoid trends; the other was a patient with manic depressive psychosis who later committed suicide.

The large number of patients with constitutional psychopathic inferiority, and also those with a normal personality but with anxiety neurosis, accounts for the poor clinical response to therapy despite the attainment of normal blood levels.

Only eight patients were free of nervous complaints or had nervous complaints which could be referred directly to the anemia. This group obtained subjective relief as soon as the anemia was corrected.

## Causes of the Anemia

Table 4 shows the important etiologic factors in the anemia. As the table indicates, among the common factors are: (1) diet deficient in meat and iron; (2) deficient gastric acidity and other gastrointestinal disturbances; (3) hypothyroidism; (4) multiple pregnancy; (5) excessive uterine bleeding or bleeding from other sources. More than one of these factors was present in almost every instance, there being an average of 2.6 causes for each case.

Table IV

Probable Causes of the Anemia

| | |
|---|---|
| (*a*) Deficient meat or iron intake | 8 cases, 32% |
| (*b*) Deficient acidity | 21 cases, 81% |
| (*c*) Hypothyroidism | 12 cases, 48% |
| (*d*) Profuse menorrhagia | 17 cases, 65% |
| (*e*) Other forms of bleeding | 6 cases, 23% |
| 1 Post partum | |
| 1 Post abortive | |
| 4 Hemorrhoidal | |
| (*f*) Multiple pregnancy | 5 cases, 18% |
| 10 or more pregnancies | 4 cases |
| 6 pregnancies in a 6-year period | 1 case |

The factor of a chronic defect in alimentary function suggested by Gray and Wintrobe [4] to explain this type of anemia is included under (2) above, but at present defies measurement.

A comprehensive concept to fuse the multiplicity of factors present in a single case is provided by Haden [5] when he uses the term *multiple nutritional deficiency disease,* defined as a defect in the intake, absorption and utilization of blood building factors. He also includes increased body need,

such as hypermetabolism in hyperthyroidism, and deficient utilization as in chronic nephritis.

### Diet for Patients with Anemia

*Directions:*

Include in the diet every day:

1. Fruits—especially oranges, grapefruit, prunes, apricots, peaches, etc.
2. Vegetables—at least one cooked and one raw vegetable daily, as spinach, lettuce, beet greens, carrots, etc.; and dried vegetables as peas, beans, lentils.
3. Cereals—preferably whole grain.
4. Bread—preferably whole grain.
5. Eggs.
6. Meats—red meats: roast beef, beef steak, beef heart, etc.; liver, kidney, sweetbreads, brain or tripe.
7. Milk—should have at least 1 pint daily.

| *Breakfast:* | *Dinner:* | *Supper:* |
|---|---|---|
| Fruit | Red meat or liver | Choose from dinner list |
| Cereal | Potato or substitute | |
| Eggs | Vegetable (cooked) | |
| Toast—butter | Salad of vegetable or fruit | |
| Milk | Bread—butter | |
| | Dessert | |
| | Milk | |

*Do not include:*

1. Condiments, pickles, relishes.
2. Fried foods, cakes, pastries.
3. Cabbage, cucumbers, radishes, onions, raw apples.
4. No canned or preserved fish.

### Associated Diseases

In addition to the diseases already mentioned, five patients (19 per cent) had hypertension or cardiac disease, seven (27 per cent) had arthritis or neuritis, and two (8 per cent) had positive blood Wassermann tests. In neither case with a positive serologic test was syphilis thought to be an etiologic factor in the anemia, nor was anti-luetic treatment alone sufficient to correct the anemia. There were no clinical signs of lues in either case. In one the anemia relapsed when the patient discontinued iron therapy; and in the other a hysterectomy was necessary because of repeated menorrhagia.

### Summary

1. A group of 26 women with hypochromic anemia was observed over a period of 27 months.

2. The term *idiopathic hypochromic anemia* is not recommended since the following factors occurred so frequently that they were thought to be of etiologic significance: deficient meat and iron intake, deficient gastric acidity and other digestive disturbances, hypothyroidism, multiple pregnancy, menorrhagia and other forms of bleeding.

3. The blood levels rose to normal under anti-anemic therapy although many of the patients continued to complain. Satisfactory clinical improvement was obtained only when a comprehensive program of gastrointestinal, endocrine and psychiatric treatment was instituted in addition to hemopoietic therapy.

4. The "indigestion" so frequently present was found to be due to spastic or irritable colon.

5. The "nervousness" was frequently due to an anxiety state, yet 24 per cent were classified as *constitutional psychopathic inferiors.*

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# FEVER THERAPY IN THE TREATMENT OF ACUTE RHEUMATIC FEVER*

By F. Lowell Dunn, M.D., F.A.C.P., and E. E. Simmons, M.D.,
*Omaha, Nebraska*

At the Fever Therapy Department of the University of Nebraska 172 arthritis patients have received treatments with the Kettering hypertherm cabinet.† Of these 12 were diagnosed as acute rheumatic fever. This small group, together with three cases from the University of Colorado, furnish the material for this report.‡

The table gives a summary of the cases, eight of which are described in somewhat greater detail in the text. Since our primary interest was the effect of fever therapy upon the course of rheumatic fever we have excluded the frequent borderline cases in which there is often clinical disagreement as to whether the disease is rheumatic fever, atrophic arthritis, or a combination of both. This fact accounts for the large number of cardiac lesions in the group. The joint manifestations were confined largely to the larger joints and there was no residual joint damage except for one case (P. M.). In six cases there were recurrent attacks of joint involvement similar to those in which fever therapy was tried.

There were eight females and seven males. The ages varied from nine to 48 years. Ten were febrile on admission to the hospital. Eight had leukocyte counts of over 10,000 on admission. Three had tonsillectomies in addition to fever therapy. In six a diagnosis of mitral stenosis was made, one had a mitral insufficiency, one had a pericarditis, and five had a systolic murmur. In none was there any record of noteworthy cardiac decompensation.

Since the group is too small to permit of any statistical observations a brief summary of eight cases has been included.

## Case Reports

*Case 1.* Mrs. A. H., aged 40, came to the hospital with rheumatic fever of six weeks' duration. She had been partially relieved by salicylates, but still had considerable pain, with swelling of the left knee and ankle. There was a rather marked mitral stenosis well compensated. She ran a low grade fever up to 101 degrees; the leukocyte count was 10,200 with 74 per cent granulocytes; 1 c.c. of blood settled

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From the University of Nebraska Fever Therapy Department, Bishop Clarkson Memorial Hospital, Omaha, Nebraska; A. E. Bennett, M.D., Director.

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‡ We are indebted to Dr. F. Ebaugh, Dr. Clarke H. Barnacle, and Dr. Jack R. Ewalt for the privilege of including the three cases from the Fever Therapy Department of the University of Colorado.

| Case | Sex | Age | Duration of Attack | Number of Attacks | Heart Lesion | Leukocytes before Treatment | No. | Fever Temp. | Therapy Total Hours | Leukocytes after Treatment | 1 c.c. Blood Settled | | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | Before Treatment | After Treatment | |
| M.A.W... | F. | 11 | 1 week | 3 | Mit. sten. | 11,600 | 3 | 103–4 | 9 | 9,800 | 24 mm.–20 min. | 24 mm.–80 min. | Symptom free. Relapse in 2 months. |
| E.K..... | F. | 38 | 1 week | 4 | Mit. sten. | 13,000 | 2<br>1 | 103–4<br>104–5 | 6<br>3 | | 24 mm.–25 min. | 24 mm.–60 min. | Symptom free. Slight flareup 2 weeks later. Gained 30 lbs. and symptom free 7 months later. |
| D.W..... | M. | 22 | 2 weeks | 1 | Pericarditis | 10,000 | 3 | 103–4 | 9 | 9,600 | 24 mm.–23 min. | 24 mm.–60 min. | Symptom free. Murmur gone. Weight gain 6 months later. |
| A.H..... | F. | 40 | 6½ weeks | 2 | Mit. sten. | 10,200 | 1<br>4 | 103–4<br>104–5 | 3<br>12 | | 24 mm.–9 min. | 24 mm.–65 min. | Pulse slower. Symptom free. |
| C.S..... | M. | 26 | 8 weeks | 3 | Mit. insuf. | 6,400 | 2 | 104–5 | 10 | 6,200 | | | Symptom free, pulse slower. No recurrence in 2 years. |
| W.M..... | M. | 35 | 2 weeks | 1 | Mit. sten. | 10,450 | 2 | 104–5 | 8½ | 7,900 | 24 mm.–19 min. | 24 mm.–17 min. | Not much if any relief. Tonsillectomy. |
| P.M..... | F. | 19 | 18 months | 1 | Sys. murmur | 7,000 | 13 | 104–5<br>103–4 | 9<br>39 | 5,000 | 24 mm.–30 min. | 24 mm.–150 min. | Slight improvement but still active. |
| B.J..... | M. | 9 | 3 weeks | 1 | Sys. murmur Extra-systoles | | 6 | 102–3 | 15 | | | | Chorea gone. Murmur disappeared. Symptom free 7 months later. |
| L.L.S.... | F. | 10 | 10 weeks | 1 | Sys. murmur Extra-systoles | 13,400 | 10 | 105–6 | 31 | | 24 mm.–90 min. | 12 mm.–120 min. | Symptom free. No heart murmur 6 months later. 21 months later recurrence chorea but no other evidence rheumatic activity. |
| H.W..... | M. | 11 | 5 weeks | 1 | Sys. murmur | | 23 | 105–6 | 46 | | | | Chorea and pain gone. Murmur disappeared. |
| M.B..... | F. | 15 | 6 weeks | 1 | Mit. sten. | 8,720 | 5 | 105–6 | 25 | 7,800 | 60 mm.–60 min. | 20 mm.–60 min. | Pain free. Tonsillectomy. |
| G.L.McI. | F. | 14 | 2 weeks | ? | Mit. sten. | 13,450 | 5 | 105–6 | 25 | 6,900 | 60 mm.–60 min. | 18 mm.–60 min. | Symptom free. |
| C.C.E.... | M. | 48 | 2 weeks | 1 | Sys. murmur | 14,000 | 5 | 105–6 | 25 | 10,400 | | | Symptom free. |
| E.L.B.... | M. | 40 | 2 weeks | 3 | | 7,200 | 6 | 104–5 | 24 | | | | Tonsillectomy, salicylates, rest, no relief. Complete relief after fever. 2½ months later symptom free. |
| L.T..... | F. | 46 | 4 months | 2 | | | 4 | 104–5 | 14 | | 24 mm.–150 min. | 24 mm.–150 min. | Complete relief. No recurrence 9 months later. |

24 mm. in 9 minutes. After her first fever treatment her pain subsided, fever lessened, and after five fever treatments of 104 to 105 degrees for three hours each she left the hospital in 21 days, pain and fever free, with 1 c.c. of blood settling 24 mm. in 65 minutes. In the 19 months since dismissal this patient aside from a mild attack of pain one month later has been symptom free.

*Case 2.* Mr. D. W., aged 22, was admitted with a history that 12 days prior he had developed red painful joints following a severe sore throat. With large doses of salicylates he was improved but still had a swollen tender left knee, a low grade fever, a small area of consolidation at the base of the left lung posteriorly, and a pericardial friction rub heard best over the base of the heart. One c.c. of blood settled 24 mm. in 23 minutes. He responded only slightly to bed rest and large doses of salicylates. After his first fever treatment he became pain free. He received three treatments of fever at 103 to 104 degrees for three hours each, and on dismissal was pain and fever free. The pericardial rub had disappeared and 1 c.c. of blood settled 24 mm. in 70 minutes. Reëxaminations during the following six months have shown no recurrences of symptoms. He has gained weight; the heart is normal in size by orthodiagraph and no murmurs are evident.

*Case 3.* G. L. McF., aged 14, was admitted to the hospital two days after developing swollen red knees. She gave a history of frequent sore throats. The present attack of rheumatic fever followed three weeks after a severe upper respiratory infection. She had fever up to 102 degrees, a mild hypochromic type of anemia with 13,400 leukocytes, 72 per cent of which were granulocytes. The sedimentation rate was 60 mm. in 60 minutes. She had an early mitral stenosis and painful swollen knees. Two weeks of bed rest in the hospital and large doses of salicylates failed to produce improvement. She was then given fever treatments, receiving five at a temperature of 105 to 106 degrees for five hours each at intervals of approximately four days. Following her first treatment the swelling of the affected joints was markedly decreased and she was able to move her legs freely. After her fifth treatment the pain and joint swelling were completely gone. Her temperature and pulse were normal, the leukocyte count was 9,400 and her blood settled 43 mm. in 60 minutes. On reëxamination 2½ months later she had been entirely free of pain and fever; her joints were still normal; there was a marked improvement in the cardiac murmur. Electrocardiograph and roentgen-ray of the heart were also normal. Her leukocyte count at this time was 6,900 with 55 per cent leukocytes and her blood settled 18 mm. in 60 minutes. This case showed marked improvement in contrast to previous failure with bed rest and salicylates.

*Case 4.* E. L. B., aged 40, with a history of a previous attack of inflammatory rheumatism 10 years ago, was admitted two weeks after the onset of the second attack, which involved in succession the left knee, left ankle and left foot. There were redness, swelling and limitation of movement. There was no evidence of heart involvement. His leukocyte count was 7,200, 55 per cent granulocytes, and the blood sedimentation rate was 18 mm. in 90 minutes. The pain improved somewhat under rest and salicylates. A tonsillectomy brought no further improvement. Since the joint symptoms persisted fever therapy was tried: six treatments of four hours each at a temperature of 104 to 105 degrees, at weekly intervals. Following his fever treatment the pain and stiffness entirely disappeared and he gained six pounds in weight. He was entirely symptom free and without joint swelling 2½ months later.

*Case 5.* Dr. C. S., aged 26, had acute rheumatic fever twice, once nine years ago, and a recurrence eight weeks before entering the hospital. The left foot and both ankles were involved. After seven weeks in bed receiving salicylates he still had a tender swollen right wrist and swollen left foot. There was a definite systolic murmur transmitted to the axilla. The pulse was somewhat rapid and did not slow

down normally after exertion. His leukocyte count was 6,400 with 47 per cent granulocytes, and the blood sedimentation rate was 12 mm. in 154 minutes. He was given two treatments of five hours each at 104 to 105 degrees at weekly intervals. Following these treatments the pain and swelling disappeared and he was able to return to his work as an intern. Five months later there had been no recurrence of symptoms. This case was relieved by fever therapy after failure following seven weeks of bed rest and salicylates.

*Case 6.* M. A. W., aged 11, school girl, with a first attack of rheumatic fever three years previously, entered the hospital one week after a recurrence. On admission she had a temperature of 102 degrees, a moderately advanced mitral stenosis, a leukocyte count of 11,600 with 87 per cent granulocytes, and blood sedimentation rate of 24 mm. in 20 minutes. Both knees were red and swollen. Following three treatments of fever at 103 to 104 degrees for three hours each at four day intervals she became pain and fever free, her pulse became normal and her leukocyte count dropped to 9,800 with 58 per cent granulocytes and a blood sedimentation rate of 24 mm. in 80 minutes. This patient felt well until two months later when, following an upper respiratory infection, she had a relapse. This relapse, treated by salicylates, bed rest and supportive measures, required four months to become inactive.

*Case 7.* B. J., aged 9, entered the hospital with a chorea following an attack of acute rheumatic fever which began four months prior to entrance. He was running a low grade fever; there was a slight systolic murmur heard best over the apex and an occasional extra-systole. He received six treatments of fever at 102 to 103 degrees for 2½ hours at five day intervals. He made a rapid recovery. Examination eight months later showed no recurrence of symptoms and disappearance of the heart murmur. This patient entirely recovered from an attack of active rheumatic fever complicated by chorea.

*Case 8.* C. C. E., male, aged 48, entered the hospital with a history of painful and swollen joints for three weeks following an upper respiratory infection. The joints of the left arm, right arm and leg had been involved in succession. On admission he was unable to use the right arm or leg because of pain and swelling. The temperature varied from 98.6 to 104.4 degrees. There was a soft systolic murmur at the apex and the pulse was irregular at times. The liver was palpable one finger below the costal margin. His leukocyte count was 14,800 with 78 per cent granulocytes, and the blood sedimentation rate was 33 mm. in 60 minutes. The electrocardiograph showed a low voltage in all leads. The heart was normal in size by roentgen-ray. He had had no previous attacks of rheumatic fever. There was improvement following large doses of salicylates and bed rest, but because of persistent joint manifestations he was given fever therapy, receiving five treatments at 105 to 106 degrees for five hours each at intervals of approximately four days. There was marked improvement at once in the joints and at the conclusion of the treatments pain, swelling and stiffness had disappeared. The temperature remained normal. The leukocyte count was 10,400 with 72 per cent granulocytes and his sedimentation rate was unaltered.

## General Comment

Of the 15 cases treated by fever therapy, three were complicated by chorea. In the group 13 became symptom free following fever therapy. In all, three had relapses: E. K. had a slight attack of joint pain lasting a few days, two weeks after her last treatment. She then gained 30 pounds and was still symptom free seven months later. Second, M. A. W. had a

relapse two months after completion of treatment which was purposely treated only with bed rest, supportive measures and salicylates. The attack lasted four months. Third, L. L. S., six months after treatment showed no murmur and no symptoms, but 21 months after treatment had a recurrence of chorea alone without leukocytosis, fever, or increased sedimentation rate. There is still no heart murmur and she is receiving further fever therapy at the present time.

One case (P. M.) showed moderate improvement although there were still rheumatic manifestations three months after fever therapy of 48 hours of fever between 103 to 105 degrees. This is the one case noted previously which showed residual joint damage.

Another case (W. M.) had essentially no improvement. After only 8½ hours of fever at 104 to 105 degrees, he refused further treatments. A tonsillectomy was also done without improvement.

Salicylates were given in 12 cases over periods of six days to seven weeks before fever therapy was tried. Although some relief was obtained, in no case was it complete.

Of the group three had tonsillectomies. One (W. M.) showed no benefit 10 days after tonsillectomy and is also recorded as a failure for fever therapy. Another (E. L. B.) received no relief within 10 days after tonsillectomy but did respond to fever therapy. The third case (M. B.) had received four treatments before the tonsillectomy, which was done as a prophylactic measure.

## Discussion

Our results indicate that fever therapy does produce definite symptomatic improvement, usually evident after the first treatment. The results obtained are commensurate with those obtained by Barnacle, Ewalt and Ebaugh [1] in chorea complicated by rheumatic carditis, and with our own unpublished observations in chorea. Sutton and Dodge [2] have reported five cases of rheumatic fever treated by mechanically induced fever with results similar to our own. In a recent personal communication from Barnacle, Ewalt and Ebaugh,[3] the incidence of carditis in their 45 cases of chorea was 42.2 per cent, that is, 19 cases. Of these 19 cases, three showed evidence of mild decompensation and one had a pericardial effusion. Immediately following pyretotherapy seven cases of carditis were considered as recovered, seven were improved, and four unchanged. The case of pericardial effusion responded satisfactorily to fever, the effusion disappeared, and he is now in school and on full activity, 20 months after treatment. Of the 19 cases of carditis 12 have been carefully checked in recent follow-up examinations: six patients showed recovery and are on full activity program, while six are improved. There are other cases which are on full activity but the investigators were unable to check them personally so they

have not included these cases in their follow-up report. They have considered all of the accepted criteria for carditis in making their diagnosis and in arriving at the therapeutic results.

It is important, however, to recognize that individual attacks of rheumatic fever have a well marked tendency to subside spontaneously. On the other hand Bland and Jones [4] in a study of 1,200 cases of rheumatic fever over a period of 13 years have stressed the persistence of low grade and sub-clinical infection with the periodic appearance of rheumatic manifestations. The tendency of rheumatic heart lesions to progress has been emphasized by many. Rothschild, Kugel and Gross [5] and others have demonstrated the persistence of Aschoff bodies in cases of rheumatic fever as evidence of protracted activity.

It seems evident that fever therapy does reduce the symptomatic activity of rheumatic fever and probably shortens the duration of the attack. The more interesting point to us is whether or not fever therapy will aid in reducing the number of cases showing subclinical activity. In this connection the table shows that in many of the cases leukocyte counts and sedimentation times become normal after fever therapy. A final determination of this point will require much longer periods of study and a larger group of cases than are available to us at the present time.

The method of producing the fever in the patient is possibly not of great importance. Our experience with the Kettering hypertherm has impressed us with the nicety of control of the temperature and the ease with which the patient can be observed and treated while in the cabinet. In this connection it is interesting to note that Bland and Jones did not produce an activation of a rheumatic process in two cases following physical hyperthermia although activation was produced with typhoid vaccine. In the 15 treated cases in our group there is only one (E. K.) in whom such an activation might have recurred. This occurred two weeks after receiving the last of three treatments at weekly intervals. She received six hours of fever in all and the activation lasted two days. From our experience there would seem to be little danger of reactivating the symptoms.

## Summary

1. Fifteen cases of acute rheumatic fever were treated with the Kettering hypertherm cabinet for periods of 8½ to 46 hours with temperatures of 103 to 106 degrees.

2. Thirteen cases received complete relief from joint pain and swelling; three cases had recurrences within 2 weeks to 21 months.

3. The possible bearing of fever therapy on the subclinical activity of rheumatic fever is discussed.

4. Because of the uncertain course of acute rheumatic fever we believe that extended studies will be necessary before final evaluation is possible.

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# THE COURSE OF HYPERTENSIVE HEART DISEASE

## III. SIGNIFICANCE OF BUNDLE-BRANCH BLOCK *

By NATHAN FLAXMAN, M.D., *Chicago, Illinois*

BUNDLE-BRANCH BLOCK is not a frequent electrocardiographic finding. Hill [1] reported 41 cases, the first 32 (0.8 per cent) of which occurred in a total of some 4000 consecutive cardiac cases examined electrocardiographically in the Royal Infirmary of Edinburgh. White [2] stated that of 9000 cases with electrocardiograms at the Massachusetts General Hospital during 15 years there were 212 (2.35 per cent) with bundle-branch block. During a period of one and one-half years at the Cook County Hospital there were 55 (3.34 per cent) cases of definite bundle-branch block in 1646 cases of organic heart disease.[3] These reports include cases due to all etiologic causes.

This type of block occurs most commonly in patients over middle-age often the subjects of hypertension.[1] The analysis of cases of bundle-branch block regardless of the etiologic cause of the underlying heart disease has been the method of choice, but is apparently as confusing as considering all the causes of auricular fibrillation under one heading to arrive at a common prognosis. For this reason the present report includes only cases of uncomplicated hypertensive heart disease which showed electrocardiograms diagnostic of bundle-branch block. Of the 786 uncomplicated cases of hypertensive heart disease seen over a five year period, 36 (4.58 per cent) had bundle-branch block as a constant electrocardiographic finding. It was the next most common graphic abnormality after auricular fibrillation (26 per cent), but only one-sixth as frequent as this arrhythmia in the course of hypertensive heart disease. Patients classified as having bundle-branch block had electrocardiograms which showed (1) definite left or right axis deviation, (2) appreciable slurring of the QRS complex with a measurable delay of over 0.1 second, and (3) T-waves pursuing a direction reversed from that of the major QRS complexes in Leads I and III. All electrocardiograms showing marked delay and slurring of the QRS complex, but failing to fulfill the other criteria mentioned above, the heterogenous group known as intraventricular, arborization, or incomplete bundle-branch block, were discarded. As to whether to interpret the typical bundle-branch block under the old (classical) or the new terminology, this issue has been omitted. My opinion, already expressed in previous writing,[4] coincides with that of O'Farrell,[5] who stated that it is doubtful from the clinical viewpoint if anything is to be gained by defining the location of lesions of the bundle with minute exactitude.

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From the Department of Medicine, Loyola University Medical School, Chicago.

The age, sex, and race of the 36 patients in this series are noted in table 1. These data agree with all previous studies in that the majority were males (32 or 88.8 per cent) over 50 years of age.

TABLE I

Percentage in the Age Groups

| Ages | White | | | | Colored | | | |
|---|---|---|---|---|---|---|---|---|
| | M. | F. | Total | % | M. | F. | Total | % |
| 31–40..... | 1 | 0 | 1 | 3.9 | 1 | 0 | 1 | 12.5 |
| 41–50..... | 4 | 0 | 4 | 14.1 | 0 | 0 | 0 | 0.0 |
| 51–60..... | 8 | 1 | 9 | 32.2 | 2 | 2 | 4 | 50.0 |
| 61–70..... | 11 | 1 | 12 | 42.1 | 2 | 0 | 2 | 25.0 |
| 71–74..... | 2 | 0 | 2 | 7.7 | 1 | 0 | 1 | 12.5 |
| Totals..... | 26 | 2 | 28 | 100.0 | 6 | 2 | 8 | 100.0 |
| | 77.8% | | | | 22.2% | | | |

As to the duration of life after the onset of cardiac symptoms, table 2 indicates the percentage of patients who were dead as compared with the known living at the end of each arbitrary period. In a previous study on the course of hypertensive heart disease,[6] it was noted that approximately

TABLE II

Duration of Disease after Onset of Cardiac Symptoms

| Duration | Deceased | | | | | | | | Living | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | White | | | | Colored | | | | White | | | | Colored | | | |
| | M. | F. | Total | % | M. | F. | Total | % | M. | F. | Total | % | M. | F. | Total | % |
| 1 Day–6 Months.. | 3 | 0 | 3 | 30.0 | 3 | 1 | 4 | 66.6 | 10 | 0 | 10 | 55.6 | 1 | 0 | 1 | 50.0 |
| 7–18 Months. | 4 | 0 | 4 | 40.0 | 0 | 0 | 0 | 0.0 | 2 | 0 | 2 | 11.1 | 0 | 1 | 1 | 50.0 |
| 19 Months–3 Years.... | 3 | 0 | 3 | 30.0 | 2 | 0 | 2 | 33.4 | 2 | 0 | 2 | 11.1 | 0 | 0 | 0 | 0.0 |
| 4–6 Years.... | 0 | 0 | 0 | 0.0 | 0 | 0 | 0 | 0.0 | 2 | 0 | 2 | 11.1 | 0 | 0 | 0 | 0.0 |
| 7–10 Years... | 0 | 0 | 0 | 0.0 | 0 | 0 | 0 | 0.0 | 0 | 2 | 2 | 11.1 | 0 | 0 | 0 | 0.0 |
| Totals..... | 10 | 0 | 10 | 100.0 | 5 | 1 | 6 | 100.0 | 16 | 2 | 18 | 100.0 | 1 | 1 | 2 | 100.0 |

80 per cent of the deceased succumbed within two years after the onset of cardiac symptoms. Of the 16 deaths in this series, 13 of the patients (81 per cent) died within two years after the onset of cardiac symptoms. Four white males, however, were alive four to six years and two white females

seven to ten years after the onset of symptoms. In Graybiel and Sprague's [7] analysis of 395 cases of bundle-branch block (hypertension given as the etiology in 154), in the entire series of the 85 living the average duration of symptoms was five years and ten months, and of the 222 fatal cases, four years and one month. Their report includes many of the etiological factors of heart disease and electrocardiographic diagnoses omitted from this analysis, which makes comparison difficult.

As to the duration of life after the appearance of congestive heart failure (table 3), 15 (93 per cent) of the 16 deceased patients died within 18 months after the signs of heart failure appeared. This percentage may be

TABLE III

Relation of Duration of Disease after Onset of Congestive Heart Failure in Relation to Discovery of Bundle-Branch Block *

| Duration | Deceased | | | | | | | | Living | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | White | | | | Colored | | | | White | | | | Colored | | | |
| | M. | F. | Total | % | M. | F. | Total | % | M. | F. | Total | % | M. | F. | Total | % |
| 1 Day–6 Months | 7 (6) | 0 (0) | 7 (6) | 70.0 (60.0) | 3 (3) | 1 (1) | 4 (4) | 66.6 (66.6) | 12 (12) | 0 (0) | 12 (12) | 66.6 (66.6) | 1 (1) | 0 (0) | 1 (1) | 50.0 (50.0) |
| 7–18 Months | 3 (4) | 0 (0) | 3 (4) | 30.0 (40.0) | 1 (2) | 0 (0) | 1 (2) | 16.7 (33.4) | 3 (3) | 0 (0) | 3 (3) | 16.6 (16.6) | 0 (0) | 1 (1) | 1 (1) | 50.0 (50.0) |
| 19 Months–3 Years | 0 | 0 | 0 | 0.0 | 1 | 0 | 1 | 16.7 | 0 | 0 | 0 | 0.0 | 0 | 0 | 0 | 0.0 |
| 4–6 Years | 0 | 0 | 0 | 0.0 | 0 | 0 | 0 | 0.0 | 1 (1) | 1 (1) | 2 (2) | 11.1 (11.1) | 0 | 0 | 0 | 0.0 |
| 7–10 Years | 0 | 0 | 0 | 0.0 | 0 | 0 | 0 | 0.0 | 0 (0) | 1 (1) | 1 (1) | 5.7 (5.7) | 0 | 0 | 0 | 0.0 |
| Totals | 10 | 0 | 10 | 100.0 | 5 | 1 | 6 | 100.0 | 16 | 2 | 18 | 100.0 | 1 | 1 | 2 | 100.0 |

* Bundle-branch block in parentheses.

compared with the general course of hypertensive heart disease where 85 per cent of the 170 deceased died within one year after the heart failure occurred.[6]

The duration of life after the detection of the bundle-branch block by graphic means was compared with the duration of life after the appearance of congestive heart failure (table 3, figures in parentheses, bundle-branch block). All of the 16 deceased patients died within 18 months after the block was recorded. Herrick and Smith,[8] in a report on 35 cases of bundle-branch block, stated that 12 or 57.1 per cent of 21 patients whom they were able to follow died within 18 months. Cowan and Bramwell [9] reported that 13 or 54.1 per cent of their 24 patients died within 18 months after the block was detected. Sampson and Nagle [10] noted especially the high fatality occurring in cases of bundle-branch block during the first year after the discovery of the lesion, and the remarkable diminution of the case fatality in the groups which survive the initial period. Lewis [11] concluded that most of the patients who exhibit this lesion are dead within two years, but some

survive many years so that the prognostic significance of the sign itself is indecisive.

There was a close and definite relationship between the congestive heart failure and the bundle-branch block in these patients. This association was first suggested by Cowan and Bramwell [9] who stated that the presence of the block indicates a definite myocardial lesion, but if unaccompanied by signs of cardiac insufficiency is not necessarily of grave prognostic significance. Kurtz [12] reported six cases of transient bundle-branch block, all with organic heart disease, and in two he stated that it was closely associated with periods of myocardial failure.

TABLE IV

Percentage of Causes of Death in 16 Cases with Bundle-Branch Block

| Causes of Death | White | | | | Colored | | | |
|---|---|---|---|---|---|---|---|---|
| | M. | F. | Total | % | M. | F. | Total | % |
| Congestive heart failure | 10 | 0 | 10 | 100.0 | 4 | 1 | 5 | 83.3 |
| Spontaneous rupture ascending aorta | 0 | 0 | 0 | 0.0 | 1 | 0 | 1 | 16.7 |
| Totals | 10 | 0 | 10 | 100.0 | 5 | 1 | 6 | 100.0 |

A survey of the causes of death (table 4) in these patients also brought out this relation of block to failure. Congestive heart failure was the cause of death in 15 (93 per cent) of the 16 deceased patients, all of whom died within 18 months after the onset of the failure and the graphic finding of the block. The exception was the youngest patient, a colored male of 31 years who was decompensated for the two years preceding his sudden death from a spontaneous rupture of the descending aorta. Analysis of the literature further bears out the relation of the heart failure to the bundle-branch block. Ten (83.3 per cent) of Herrick and Smith's [8] 12 deceased patients died of cardiac failure. Nine (81.8 per cent) of Cowan and Bramwell's [9] 11 deceased patients with hypertensive heart disease died of congestive heart failure. The important factor in these patients with hypertensive heart disease with bundle-branch block was the congestive failure and not the block, in spite of the fact that the graphic finding was typical and persistent in all cases. The importance of congestive heart failure in relation to hypertension and the heart has been emphasized on two previous occasions.[6, 13]

Those additional pathological findings which are common in hypertensive patients were found to be very infrequent in hypertensive cases with bundle-branch block. Gallop rhythm was present in five (13.8 per cent) of the 36 patients. All five were males, and 18 months after the detection of the bundle-branch block two were alive. Campbell and Suzman [14] cited

the case of a 52-year-old male with cardiac symptoms of six weeks' duration and a blood pressure of 210 mm. of Hg systolic and 130 diastolic, who had gallop rhythm and bundle-branch block. Nine months later the gallop and the block both had disappeared. They suggested that the gallop rhythm was due to the bundle-branch block, but my cases neither suggest nor bear out such a relationship.

Auricular fibrillation was present in only two (5.5 per cent) of the 36 patients, both white males; one white male (2.7 per cent) had a cerebral hemorrhage, and another (2.7 per cent) had a coronary occlusion during the course of the disease. Only one patient (2.7 per cent), a white female, had diabetes mellitus, which was of seven years' duration.

## Comment

The pathogenesis of bundle-branch block in hypertensive heart disease is indefinite. In an extended review of the literature Rosenthal [15] found no discussion of this topic. From his studies he concluded that the degenerative changes which occur in the bundle are explained by an increased tonicity of the small arteries and the arterioles which brings about prestasis and stasis in the precapillaries and capillaries.

There are probably many examples of longevity with bundle-branch block which have not been reported. The Bishops [16] cited the case of a 47 year old woman with a blood pressure of 200 systolic and 105 diastolic who had dyspnea of one year's duration when the block was first recorded. Eleven years later she was still well and still showed the bundle-branch block. Sampson and Nagle [10] reported one patient still in reasonably good health 12 years after the discovery of the lesion. In the present series one woman was alive 10 years after the block was noted.

## Summary

Bundle-branch block, graphically noted in the course of hypertensive heart disease, occurred in 36 (4.58 per cent) of 786 patients with this disease. It appeared to have no definite diagnostic or prognostic significance in these patients. The block was considered as only an unusual electrocardiographic finding in hypertensive heart disease, the mechanism of which was not clear. The prognosis of the hypertensive patient with bundle-branch block was that of the underlying heart condition, particularly in relation to the occurrence of congestive failure. Sixteen (44.4 per cent) of the patients died within 18 months after the bundle-branch block was graphically noted, and in all except one the cause of death was the congestive heart failure. There was a very close relationship between the bundle-branch block and the congestive heart failure in the insufficient hypertensive heart.

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# THE ASSOCIATION OF ADENO-MYO-SARCOMA OF THE KIDNEY (WILMS TUMOR) WITH ARTERIAL HYPERTENSION *

By J. Edmund Bradley, M.D., and M. C. Pincoffs, M.D., F.A.C.P.,
*Baltimore, Maryland*

The rôle played by disease of the kidneys in the pathogenesis of arterial hypertension has always enlisted the interest of clinicians. Bright drew attention to the fact that in cases of albuminuria there was frequently found hypertrophy of the heart. Traube and Cohnheim correctly interpreted the cardiac hypertrophy as due to increased blood pressure. The association of arterial hypertension with Bright's disease was thus early established. The nature of the relationship was variously interpreted, but the most widely accepted viewpoint was that the disease of the kidney was primary and that from it arose unknown consequences that brought about an abnormal elevation of the blood pressure.

With the gradual differentiation as an entity of essential hypertension or hyperpiesia, and the acceptance of the fact that in this disease the elevation of blood pressure precedes often by years any detectable renal lesion, a first important step was taken away from the conception of an exclusively renal etiology of high blood pressure. There remained, however, as firmly founded, the relatively constant association of acute and chronic glomerulonephritis with arterial hypertension. The most commonly accepted explanation of this association still is that the kidney damage is the primary event and that the arterial hypertension is secondary. On the other hand, in the last 15 years an important group of investigators of this problem have put forward the hypothesis that the disease which we call glomerulonephritis is in fact a diffuse vascular disease characterized by angiospasm. The arterial hypertension according to this theory is a consequence of widespread arteriolar and capillary constriction due to vascular disease. The renal lesions are likewise a product of vascular disease in the kidney; ischemic according to some authors, or primarily due to damage to glomerular capillaries according to others. Those who have accepted this point of view are therefore of the opinion that the kidney lesions are secondary, both in essential hypertension and in glomerulonephritis, and that in neither condition is kidney damage an essential factor in the pathogenesis of the accompanying hypertension. The more radical opponents of any renal origin of hypertension will not even concede that the kidney damage in such conditions as chronic pyelonephritis and polycystic kidneys gives rise to the arterial hypertension which accompanies these conditions in a significant percentage of the cases.

* Read in part before the Association of American Physicians, Atlantic City, May 1937.
From the Departments of Pediatrics and Medicine, University of Maryland School of Medicine.

Such extreme opinions are no longer tenable in view of the developments of the last few years. The earlier failures to produce arterial hypertension experimentally in animals by various types of induced kidney damage have been followed by the development of successful methods. Of these the most dependable is that of Goldblatt [1] which consists essentially of a partial occlusion of the renal arteries by means of special clamps. The elevation of the blood pressure in such animals is of marked degree and may be sustained over months or even years. The removal of the clamps in the earlier stages of the process will result in the subsidence of the blood pressure to normal levels. The well controlled work of Goldblatt has definitely shown that in animals this type of interference with the blood supply of the kidneys will produce an arterial hypertension. Moreover recent careful studies of large series of cases of polycystic kidney and of chronic pyelonephritis have definitely shown that an abnormally elevated blood pressure accompanies these conditions at all ages in a percentage of cases too large to be due to coincidence. Further, in autopsied cases of these conditions no cause for the hypertension, other than the renal lesions, has been found. Since the incidence of the hypertension, especially in the early age groups, is too high to be explainable as a coincidental occurrence of so-called essential hypertension, these studies point strongly towards a renal causation for the hypertension in these primarily renal diseases. However, since the lesions are bilateral there is no opportunity to obtain further evidence through observation of the effects on the arterial hypertension of the surgical removal of the presumably causative lesion.

The existence of a renal form of hypertension in man might be considered finally proved if a renal lesion were discovered in man, whose presence was constantly associated with arterial hypertension and whose surgical removal constantly led to the fall of this pressure to normal levels. In five consecutive cases, in infants and young children of the so-called embryonal adeno-myo-sarcoma of the kidney (Wilms tumor) we have observed the concurrence of arterial hypertension. In two of these cases we were able to observe the effect of operative removal of the tumor and found in each that a marked lowering of the blood pressure occurred and that with recurrence of the growth the blood pressure again rose to higher levels. These observations suggest that through a study of a more extensive series of such cases important evidence as to the existence and the nature of human renal hypertension may be obtained. For this reason the data on these cases are felt worthy of report.

## Case Reports

*Case 1.* J. C., a white female child, aged two years, was admitted to the University Hospital because of a mass in the right abdomen, noted first nine days previously and because of hematuria of 24 hours' duration. The history otherwise was of no significance. On examination the mass was found to fill the right abdomen from the costal margin to the iliac crest. It caused a visible protrusion of the abdominal wall. An intravenous pyelogram showed no filling on the right side.

The blood pressure of this child (figure 1) and of the later cases was determined with a mercury manometer with a 3 inch cuff with due care to record only pressures taken when the child was quiet. Blood pressures are taken routinely on the pediatric service. A pressure of 90 mm. systolic and 60 diastolic is considered normal for this age.[2, 3, 4]

This child's pressure before operation was between 150 mm. and 180 mm. systolic and the diastolic was consistently over 110 mm. The consistency of the elevation of the pressure is noteworthy. Frequent readings throughout the day were taken but no evidence of abrupt variations nor of paroxysmal elevations was obtained.

Study of the renal function showed a two hour phthalein excretion of 80 per cent: the specific gravity in the Mosenthal test ranged between 1.018 and 1.032: the non-protein nitrogen was 21 mg. per cent. The hypertension, therefore, bore no relation to faulty renal excretory function.

The heart on physical examination and by teleoroentgenogram was not enlarged and the sounds were normal. The electrocardiogram, however, showed left axis deviation and a deep $Q_3$. The retinal arteries showed no change.

Nineteen days after admission an attempt was made to remove the tumor surgically. The greater part of the encapsulated mass occupying the site of the right kidney was taken out, but because of the friability of the tissue and the bleeding encountered a portion had to be left. Within a few days after operation the child showed definite improvement. She was alert, interested in her playthings and took nourishment with good appetite. This period of clinical improvement lasted somewhat over two weeks. Then she began to drift down hill. Palpable evidence of

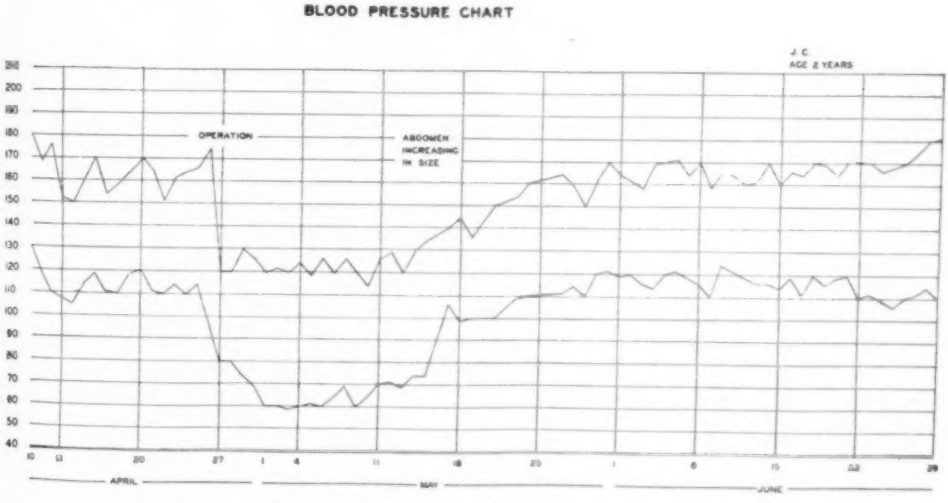


FIG. 1. Blood pressure chart in Case 1.

recurrence was noted at the end of the third week and by the time death occurred from cachexia and bronchopneumonia, three months after operation, the right abdomen was again filled with a large mass. It may be seen on the chart (figure 1) that following operation during the period of clinical betterment the blood pressure was distinctly lowered, falling to 130 systolic and 100 diastolic, but that as the tumor again increased in size the blood pressure gradually rose and reached its former high level, in a period when the child exhibited marked emaciation and weakness.

The tumor tissue removed at operation weighed 500 gm. Sections (figure 2)

showed numerous epithelial elements arranged in tubular, cystic and glomerulus like structures, embedded in a matrix of myxomatous and spindle cell connective tissue. Muscle fibers were noted in frozen sections. The tumor tissue was very vascular. Large areas of necrosis and of hemorrhagic infiltration were observed. The pathological diagnosis was: "A typical embryonal adeno-myo-sarcoma, or Wilms tumor."

FIG. 2. Section from tumor mass in Case 1.

In an attempt to discover the nature of the pressor action of the tumor, gross serial sections of the mass were carefully studied and numerous blocks taken and sectioned to see whether adrenal medullary or cortical tissue or aberrant chromaffine cells were present. None was found. Moreover, immediate extraction of two samples of fresh tumor tissue was carried out by Dr. Wm. H. Schultz. The pressor effects of these extracts on intravenous injection were tested in young dogs and found to be nil. The extracts gave no color reactions for adrenalin and no adrenalin reaction on intestinal or virginal uterus muscle strip preparations.

An autopsy of this patient showed a massive tumor recurrence weighing 1860 gm. The left kidney and both adrenals were found normal grossly and microscopically. The heart weighed 50 gm. which is normal for this age. The larger arteries showed no gross evidence of arteriosclerosis.

*Case 2.* B. C., a colored male child, aged two years, was admitted to the University Hospital in May 1935, because of hematuria of 48 hours' duration. The past history contained nothing significant aside from rather numerous respiratory infections. The child was normally developed for the age. On palpation of the abdomen a globular mass was felt on the right side extending from the costal margin to the crest of the ilium. An intravenous pyelogram showed marked dilatation of the pelvis and calyces of the greatly enlarged right kidney. For four days after admission the patient had a severe hematuria with a considerable total loss of blood.

This child's systolic pressure varied between 120 and 140 mm. and the diastolic between 80 and 100 mm. (figure 3). This is a well marked though not severe hypertension, when one considers that a pressure of 90 systolic and 60 diastolic is normal

for this age period. This elevation of blood pressure was continuous during the month preceding operation.

As in the first child there was no evidence of depression of renal function. The phthalein output in two hours on two tests was 65 per cent and 80 per cent. The non-protein nitrogen was 26 mg. per cent. A range of specific gravity between 1.012 and 1.028 was noted.

The physical examination of the heart and the teleoroentgenogram did not give evidence of any cardiac enlargement. The electrocardiogram did not show left axis deviation and was otherwise also quite normal. The retinal arteries showed no changes.

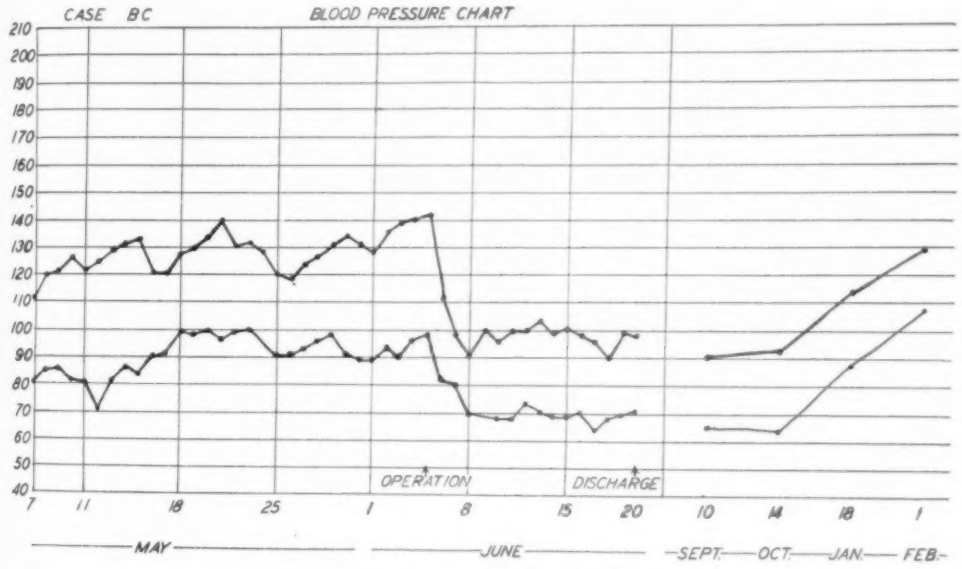


FIG. 3. Blood pressure chart in Case 2.

One month after admission an operation was performed; a large encapsulated tumor arising from the right kidney was found. Kidney and tumor were removed *in toto* (figure 4). The child stood the operation very well; the post-operative healing was uneventful and the child was discharged from the hospital 15 days later. Thereafter the patient was seen at intervals in the out-patient department over a period of seven months. The blood pressure was normal, 88 systolic and 60 diastolic, until in the sixth month when it began to rise and in the seventh month again reached its former hypertensive level. At this last visit a palpable mass was noted at the site of the former tumor. Unfortunately, the parents refused to return the child to the hospital; moreover they moved their residence and all attempts to trace this case further were fruitless.

The tumor removed at operation from this case was a globular mass replacing the middle section of the right kidney. The growth was made up of rather uniform oval or spindle cells, without bundling, but instead rather indiscriminately scattered through a fibrous stroma. Hyalinized areas were observed; vascularity was not a prominent feature. Only scant adenomatous structures were noted. The pathological diagnosis was: "A fibrosarcomatous variant of the Wilms tumor."

*Case 3.* R. R., a white male infant, aged two months, was admitted to the Mercy Hospital with the history of increasing abdominal enlargement for one month.

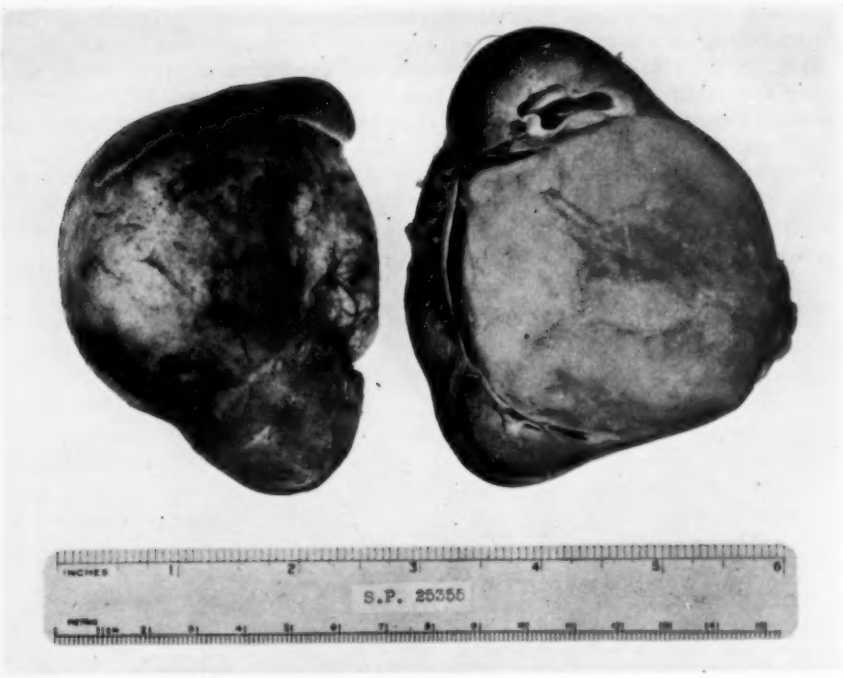


FIG. 4. Right kidney containing tumor from Case 2.

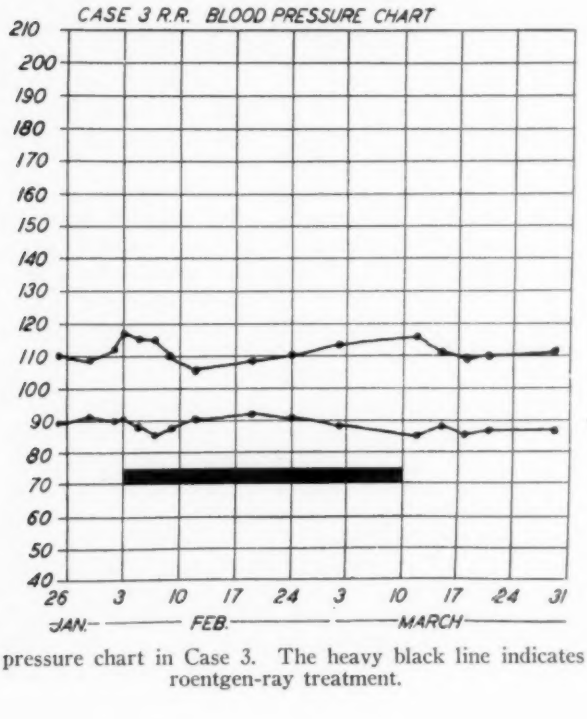


FIG. 5. Blood pressure chart in Case 3. The heavy black line indicates the period of roentgen-ray treatment.

The child showed marked malnutrition and the greater part of the abdomen was occupied by a large firm mass. The presence of a few red blood cells in the urine and the lack of filling of the right pelvis and ureter on intravenous pyelography indicated that the mass arose from the right kidney.

Sixteen days after admission, through the kindness of Dr. Edgar Friedenwald, one of us was enabled to begin determinations of this child's blood pressure (figure 5). It was found to range between 106 and 116 mm. of Hg systolic and between 85 and 90 mm. diastolic. The normal mean pressure for this age as determined

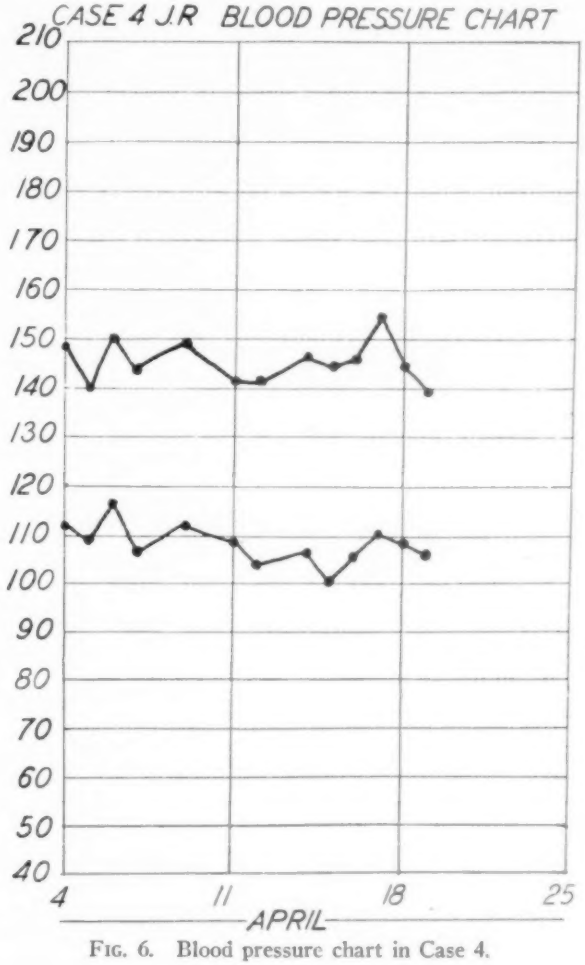


FIG. 6. Blood pressure chart in Case 4.

in a series of cases (by J. E. B.) is 78 systolic and 56 diastolic. Hence this child's pressure in spite of its cachectic state was elevated to a level corresponding to 150 systolic and 100 diastolic in an adult. The level of the pressure was not affected by a period of irradiation of the growth which very greatly reduced its size. This treatment together with small transfusions was given in preparation for operation but three months after admission the infant was carried off by an acute diarrhea.

At autopsy the remaining mass weighed only 110 gm. The right kidney was almost completely destroyed. The tumor tissue showed marked necrosis, cystic

degeneration and hemorrhagic infiltration. The microscopic sections showed sparse epithelial tubular-like structures in a stroma of spindle cells and myxomatous tissue. The left kidney and both adrenals were normal.

*Case 4.* J. R., a white female child, aged two years, was admitted to the Maryland General Hospital in November 1936, because of a painless enlargement of the abdomen of six weeks' duration. On examination a large nodular mass was found occupying most of the left half of the abdomen. An intravenous pyelogram showed no visualization of the left kidney pelvis. The urine examinations were negative. The non-protein nitrogen was 22 mg. per cent. Operation revealed a large tumor of the left kidney which had broken through its capsule in several places. This was removed. Recovery was uneventful. Five months later the patient was readmitted with a large palpable recurrent mass. At this time through the kindness of Dr. R. P. Bay, one of us was able to make repeated determinations of the blood pressure (figure 6). These showed that the systolic pressure ranged consistently between 140 and 150 mm. of Hg and the diastolic between 100 and 112 mm.

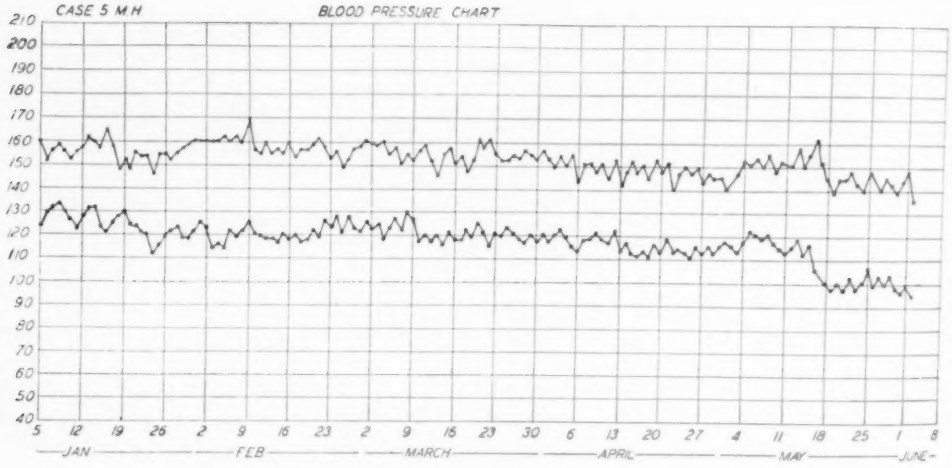


FIG. 7. Blood pressure chart in Case 5.

The tumor from this patient was partly cystic and partly solid. A gelatinous tissue occupied the cystic area. The more solid tissue contained numerous epithelial elements surrounded by a fibromuscular stroma very characteristic of embryonal adeno-myo-sarcoma or Wilms tumor.

*Case 5.* M. H., a colored male child, six years of age, was admitted to the University Hospital on January 5, 1937 with a complaint of enlargement of the abdomen which had been first noted approximately one year earlier. During this interval vague complaints of abdominal pain of no definite type had been made. Within the two months prior to hospitalization, the abdomen had greatly increased in size. It was stated that constipation had been present since birth and that the child had suffered with occasional respiratory infections. Otherwise the history contained nothing of interest.

On examination the child was well nourished. A mass was palpable in the left flank extending to slightly beyond the midline medially and from the costal margin above, downward almost to the crest of the ileum. It was globular, hard, freely movable, non-sensitive and of even consistency. The edge of the liver extended two fingers-breadth below the costal margin in the nipple line. Both intravenous and

retrograde pyelography failed to show any filling of the left kidney pelvis. The right ureter and kidney pelvis were normal in outline. A clinical impression was that the tumor arose from the left kidney and was probably a Wilms tumor.

The blood pressure in this child on admission was 160 systolic and 124 diastolic (figure 7). The pressure remained consistently elevated throughout the five months' stay of the patient in the hospital. As terminal cachexia set in there was an appreciable decrease in both systolic and diastolic pressures, but, as may be seen from the blood pressure chart, neither ever attained normal levels. The steadiness of the blood pressure level was rather striking for a child of this age. On one occasion readings were made every two hours for sixteen hours (figure 8) and showed very slight variations.

Very numerous urinary examinations in this patient's case failed to show any abnormalities. Concentration tests showed a range of specific gravity between 1.024 and 1.030 on one test and of 1.012 and 1.023 on a second test. The urea clearance was 80 to 87 per cent. The phthalein output was 70 per cent in two hours; the nonprotein nitrogen 24 to 32 mg. per cent.

Examination of the heart showed clinically no evidence of enlargement, nor change in the rhythm or character of the heart sounds. The electrocardiogram was reported as normal and the teleoroentgenogram showed a normal cardiac outline. The examination of the ocular fundi on admission did not show any vascular changes, but later in the patient's course it was noted that there was some increased tortuosity of the arteries and an increase of the light reflex.

For a period of six weeks after admission the child was treated with roentgen irradiation of the tumor. Nevertheless, during this time the liver increased markedly in size, extending downward into the right flank. The left eye began to show proptosis and vision in this eye was lost. These changes were taken to indicate metastatic growths in the liver and in the left orbit. Roentgen-ray of the skull did not show any bone metastases.

An exploratory laparotomy now revealed a very vascular mass involving the left kidney region and extending across the midline to blend with an ill-defined growth apparently invading both the liver and the right kidney. No tumor tissue was removed.

The subsequent course was entirely downhill with increasing cachexia, increasing enlargement of the abdomen and extension of the orbital metastases downward into the nasal cavity. The child died 151 days after admission. Because of the interest attached to the widespread metastases in this case, complete autopsy findings are appended.

*Autopsy:* June 3, 1937. Pathologist: Dr. M. S. Sacks. The body is that of a young negro male child measuring 105 cm. in length. It is markedly emaciated. The head and scalp show no changes. There is marked proptosis of the left eyeball. The right eye shows no changes. Examination of the mouth reveals a small cauliflower-like lesion in the hard palate which measures approximately 1 cm. in diameter. The chest is emaciated and the abdomen is markedly distended. There is a partially healed left paramedian incision. The external genitalia reveal no chang There is no external lymphadenopathy, jaundice or edema.

The subcutaneous tissue is practically devoid of fat. The musculature of the thorax and abdomen is pale, thin and flabby. On opening the peritoneal cavity there is a gush of clear yellow serous fluid. This is present to the extent of about 200 c.c. The liver is seen to occupy almost the entire upper half of the abdomen. It extends down for a distance of 12 cm. below the right midclavicular line. There is a second mass noted in the left flank and as a result of the presence of these masses the entire gastrointestinal tract is pushed downward to the right.

The anterior chest plate is removed and both pleural cavities are seen to be free of fluid or adhesions. The pericardium is smooth and glistening but is somewhat

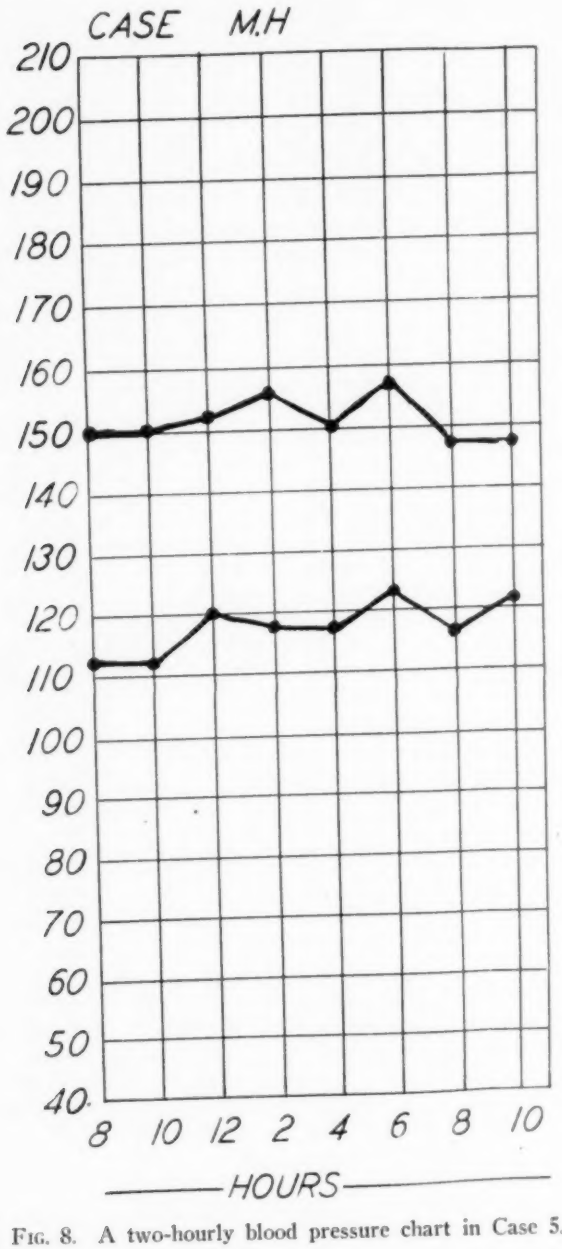


FIG. 8. A two-hourly blood pressure chart in Case 5.

distended by an excess of clear yellowish serous fluid. The thymus is quite small; it occupies its usual position and reveals no gross changes.

*Heart:* Weight 110 grams. The epicardium is smooth and glistening. The heart appears to be of normal size. There is some dilatation of the right ventricular cavity. The myocardium has a homogeneous pinkish gray appearance and presents

no gross pathologic change. The endocardium both mural and valvular shows no change.

*Aorta:* The aorta is small—of normal caliber, very elastic and presents no intimal changes.

*Lungs:* Right weighs 250 grams—left 200 grams. Both lungs are removed together with the trachea. The trachea is patent throughout and examination of its mucosa reveals no pertinent changes. The tracheobronchial lymph nodes are found somewhat enlarged; these have a dark red, almost hemorrhagic appearance; they are soft and measure up to 2 cm. in length. Left lung: Examination of the pleural surface reveals it to be glistening but to be studded by multiple nodules of varying size, some of which are sessile and some pedunculated. These nodules vary in size up to 5 cm. in diameter. They are soft and have a pinkish red appearance. Some have a distinctly cauliflower-like appearance. They are found on all surfaces of the lung. On cross section all lobes have a pinkish gray dry appearance and numerous nodules are noted projecting from the cut surface. The lobes are distinctly less crepitant than normal. The right lung presents an essentially similar appearance. One nodule on the pleura of the right lung has a multilocular cystic appearance. On puncturing these cysts they are seen to contain air.

*Liver:* This organ is tremendously enlarged and weighs 2,700 grams. Its contours are markedly distorted by the presence of numerous, roughly circular, metastatic nodules measuring up to 7 cm. in diameter. These nodules are soft, have a yellowish gray color, with thin red streaks running through them, which tends to give them the appearance of the cut surface of an orange. On section it is noted that these masses have displaced the vast majority of the parenchymal cells. They have a similar appearance on cut surface. The gall-bladder and biliary passages present no gross pathologic change.

*Kidneys:* Right weighs 110 grams—left 1,000 grams. Right kidney: This organ has been markedly compressed and flattened in its anteroposterior diameter by the overlying markedly enlarged liver. It can be readily separated from the overlying liver. The capsule strips with ease revealing a pale grayish-red smooth surface. On cross-section the architecture is seen to be very indistinct. The calyces and pelvis are of normal size—smooth and glistening—and show no changes. The ureter is patent throughout and of normal size.

Left kidney: This kidney measures 18 by 12.5 by 7 cm. The greater part of the kidney parenchyma has been replaced by a large firm grayish yellow tumor mass. At the lower pole may be distinguished a small fragment of pinkish red tissue which bears a resemblance to normal tissue. The entire tumor mass and kidney are covered by a dense grayish white capsule. The ureter, which is of normal size, may be seen entering at the lower pole of this mass. On cross section the cut surface of the tumor has a somewhat lobulated, yellowish-gray, moderately firm appearance. At the extreme lower pole may be noted a section of recognizable kidney parenchyma.

*Adrenals:* The adrenals occupy their normal position but both are markedly flattened out. The right adrenal on section possesses a definitely recognizable cortex and medulla. The left adrenal can be separated with ease from the underlying kidney tumor mass and it possesses a grayish-brown homogeneous appearance on cut section, without distinguishable cortex and medulla.

*Bladder:* The bladder is small, contracted, empty. Examination of its mucosa reveals it to be smooth, gray and glistening.

*Spleen:* Weight 70 grams. It is firm, the capsule is smooth and taut. On section the pulp is dark red. The Malpighian bodies may be readily distinguished.

*Pancreas:* Weight 30 grams. There is no external abnormality and cross section reveals no change from normal.

*Gastrointestinal Tract:* The esophagus is patent throughout and reveals no changes. The stomach is contracted. The rugae are prominent but no gross lesions are evident. Examination of the mucosa and wall of the remainder of the intestinal tract reveals no changes until one comes to the descending colon. The wall here is somewhat thicker than normal. The mucosa has an edematous appearance and under the serosa may be noted multiple small petechia-like areas occurring in large numbers.

*Lymph Nodes:* The peripancreatic lymph nodes display a red hemorrhagic appearance; they are somewhat larger than normal. On cross section they present a red granular surface.

*Head:* Not opened.

*Anatomical Diagnosis:*

Embryoma (Wilms tumor) left kidney, with metastases to liver, lungs, parietal and visceral pleurae, palate, left orbit, peri-pancreatic and tracheo-bronchial lymph nodes; proptosis, left eyeball; ascites (200 c.c.); pulmonary atelectasis, partial, bilateral; partially healed left para-median surgical incision; emaciation, extreme.

*Microscopic Notes:*

*Heart:* This section of left ventricular myocardium shows well preserved muscle fibers which are apparently moderately hypertrophied. The epicardium is seen to contain a moderate amount of fat. Cross sections of coronary vessels seen here show no thickening of their walls. There is no scarring or increase in interstitial tissue.

*Lungs* (two sections): These sections show an air containing tissue. Occasional groups of alveoli are collapsed but these seem to be in proximity to tumor nodules. The interalveolar capillaries are congested. The bronchioles are normal histologically. Scattered throughout the parenchyma and also arising from the visceral layer of pleura are noted fairly numerous nodules composed of neoplastic tissue. The nodules are of varying sizes and display a structure which varies from a densely cellular compact tissue to one composed of loose, anastomosing cords of cells. These nodules are extremely vascular and are composed of cells possessing no distinct cytoplasmic boundaries, which have a small, somewhat vesicular oval nucleus. Such cells form wavy strands of tissue intermingling in all directions. No distinct epithelial elements are present. A very scant, underlying acidophilic stroma is noted in some areas.

*Liver:* Three sections are examined. One shows the uninvolved parenchyma and the other two are portions of the large metastatic nodules. The parenchyma proper displays no disturbances of architecture. The liver cords are perhaps somewhat compressed and there is slight congestion of the central venules. Scattered cells show mild fatty changes. The tumor nodules have a distinctive structure. One sees here narrow, anastomosing bands of cells, with elongated spindle-shaped nuclei often displaying a prominent nucleolus. These bands are separated from each other by a pale, relatively acellular, loose alveolar-like type of tissue. The nodules are quite vascular. They have apparently compressed and destroyed the liver parenchyma previously present.

*Spleen:* This section shows a cellular pulp which is moderately congested. The venous sinuses are patent. Malpighian bodies are numerous and of normal appearance. Some display germinal follicles. No evidences of neoplasm noted.

*Pancreas:* This section reveals evidence of moderate postmortem autolysis affecting the acinar and islet epithelium. No vascular wall thickening is present.

*Large Intestine:* This section shows a well preserved mucosa and no histological changes in the other layers. Several arterioles are observed in the mesentery and none of these shows any marked intimal thickening.

*Kidney:* (*a*) Left—This section reveals no disturbance of the normal architectural patterns. The glomeruli are numerous. Epithelium of convoluted tubules shows moderate swelling and some granularity of the cytoplasm. No interstitial changes are present. The arterioles display no changes.

(*b*) Right—This section displays a narrow peripheral strip of kidney parenchyma with several processes extending downward into a tumor mass. The glomeruli are small and compressed and there is a marked increase in interstitial fibrous tissue. Many tubules are obliterated and those remaining are narrowed and compressed. The tumor boundary is well defined. The neoplasm itself shows an abundance of relatively cellular fibrous tissue between the bundles of which are narrow strands of hyperchromatic cells of a similar appearance to those described above. No epithelial elements are present here and the striking thing is the abundance of fibrous tissue.

*Adrenals:* Three sections are studied, representing portions of both adrenals. These sections reveal narrowing of the entire gland which is particularly marked on the left. The narrowing results in giving the glands an appearance of being all cortex. Moderate postmortem autolysis is noted. Several small cortical adenomas are present. No evidence of neoplastic change present.

*Lymph Nodes:* Three sections examined. One displays no neoplastic involvement, but instead shows a markedly congested medullary portion (probably peripancreatic in location). In the other sections neoplastic tissue, chiefly fibrous in nature, has invaded the glandular structure.

### Assay of Tumor Tissue

Through the kindness of Dr. John C. Krantz, Jr., of the Department of Pharmacology, the following studies were made to determine the presence of adrenaline or of any other pressor substance in the tumor tissue.

Twenty-five grams of fresh tissue representing different portions of the tumor were finely minced, agitated briskly for one-half hour with 100 c.c. of normal salt solution, strained and centrifuged. The faintly opalescent liquid obtained gave a positive test for adrenaline with the Folin-Cannon-Denis reagent. The intensity of blue corresponded to about a $1:10^5$ adrenaline. This reaction is not specific for adrenaline. The Vulpian reaction ($FeCl_3$ green color—specific for catechol derivatives) was negative. Comessatti reaction (pink with sodium acetate and mercuric chloride) was negative.

Dog—light ether anesthesia—normal carotid B.P. 150 mm. Hg.

| | | |
|---|---|---|
| Injections | 0.5 c.c. $1–10^4$ adrenaline | 20 mm. rise in B.P. |
| | 1.0 c.c. $1–10^5$ adrenaline | 4 mm. rise in B.P. |
| | 1.0 c.c. tumor extract | no change |
| | 2.0 c.c. tumor extract | no change |
| | 5.0 c.c. tumor extract | no change |
| | 5.0 c.c. tumor extract | no change |
| | 5.0 c.c. tumor extract | no change |

The dog's B.P. was still sensitive to adrenaline.

Ten c.c. of the extract were shaken briskly with activated charcoal (adsorption of histamine, adenosine, adenylic acid and other depressors). The filtrate (5 c.c.) was twice injected into the same dog—there was no rise in blood pressure.

The animal experiment along with the negative chemical tests indicate the absence of adrenaline in the tumor, and of any pressor substance extractible by slightly acidulated saline solution.

## Discussion

The kidney is the most frequent site of neoplastic disease in infancy and childhood [5, 6] and tumors of the kidney account for approximately 25

per cent of all the malignant growths occurring in this period. The commonest renal tumor at this age is a mixed tumor, named from its structure embryonal adeno-myo-sarcoma, but also frequently designated as the Wilms' tumor. Mixter,[7] in computing the frequency of this tumor, found 41 renal growths in 22,000 admissions to the Children's Hospital in Boston, of which 30 were of the Wilms type. These tumors are, as a rule, encapsulated, oval to globular in shape, solid and variously subdivided into lobules. The tumor formation is usually separated by a layer of fibrous tissue from what is left of the kidney in which it has developed. The kidney tissue is usually atrophied to a greater or lesser extent by pressure but otherwise shows no abnormalities. Microscopically the growths are composed of so many different types of tissue and exhibit such different degrees of differentiation that no single morphological description will apply. In general, it may be stated that they are composed of a mixture of tissues in which are found nonstriated muscle, fibrous and myxomatous connective tissue and complex arrangements of epithelium suggesting glomeruli and tubules. Adipose tissue and cartilage may also be found. The origin of the tumor is undoubtedly from fetal rests. Wilms, Birch-Hirschfeld, Busse, Ewing and others have offered various theories as to their origin, the only resultant agreement being as to the embryonic nature. The tumor is essentially malignant, metastases occurring mainly by the blood stream and usually affecting the liver and lungs, rarely the opposite kidney. Widespread metastases, such as occurred in M. H. (Case 5), are unusual. Since the growth of these tumors is usually asymptomatic, they are, as a rule, quite large when diagnosed. Therapy by irradiation followed by operation is recommended but rarely results in cure.

We have not found in the literature any earlier observations upon the association of arterial hypertension with embryonal adeno-myo-sarcoma. We do not, of course, feel that the constancy of this association can be considered established until a large series of cases has been observed. It seems important that this fact be determined for if the association is a constant one it will become more likely that the tumor tissue itself is the cause of the hypertension, whereas if hypertension is found in only a certain percentage of cases with Wilms' tumor, as is the case in the hypertension of polycystic kidneys, pyelonephritis and urinary back pressure, it will appear more likely that its cause must be sought in some occasional complication of the tumor growth such as disturbances in its arterial supply, necrosis of tumor tissue, etc. Our own endeavors to find a pressor substance in the tumor tissue or the inclusion within it of aberrant chromaffine tissue have given negative results.

The question arises whether the hypertension might be due in these cases to the kidney tissue damaged by pressure from the tumor growth rather than by the tumor tissue itself. In our second case, B. C., the entire kidney

containing the growing tumor was removed surgically (figure 4); nevertheless, the recurrent growth of tumor tissue led to a return of the hypertensive state.

That the hypertension in these cases was in some way a consequence of the tumor growth seems to us a reasonable conclusion from the facts presented. In the first place, the possibility that the association of the two conditions was an accidental one must be considered very remote. Hypertension in infancy [8, 9, 10, 11] is quite a rarity and when found has usually been accompanied by glomerulonephritis or chronic pyelonephritis or in isolated cases by adrenal medullary tumors, brain tumors or coarctation of the aorta. In our cases, no evidence of nephritis was present in life, renal function was unimpaired and in three cases at autopsy the remaining kidney was histologically normal. In these three autopsied cases likewise the adrenals showed no abnormality. There was no evidence of urinary back pressure. In two cases the aorta was examined and found normal. There was no evidence to suggest an intracranial lesion. In brief, then, complete examination in three cases and such data as we possess on the other two do not afford any other explanation than the tumor for the hypertension.

Moreover, in two cases the removal of the tumor was followed by a significant fall in blood pressure. In the second case, in which the removal was apparently complete, the blood pressure fell to normal levels and remained there for some months. Finally in both of these cases recurrence of the tumor growth was accompanied by a return of the hypertensive state.

It is of particular interest, we feel, that a unilateral renal lesion should cause elevation of blood pressure. In experimental hypertension a permanent elevation has rarely been obtained except when both kidneys have been damaged. It is of interest also that the level of the elevated blood pressure is quite steadily maintained.

We feel that the tumor tissue in these renal tumors has a property possessed by renal tissue when it has been altered by certain types of damage—that is, the property of causing, through as yet unknown mechanisms, an abnormal elevation of arterial pressure. These observations of the relation of these renal tumors to hypertension furnish new support to the view that there are clinical forms of high blood pressure of primary renal causation.

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# MEDICAL SHRINES *

## Remarks at the Annual Banquet of the American College of Physicians 1937

By Logan Clendening, M.D., F.A.C.P., *Kansas City, Missouri*

Tonight it is my purpose to discuss with you some memories of our past—the past of medical science and of medical service. Specifically, I want to discuss the memorials of the men and institutions that made that past—memorials in the form of hospital or university buildings, or in the form of statues of the great men and women of our tradition, their birth houses appropriately marked, or their graves properly inscribed.

And I want to suggest that it is a function of this College to encourage the memorialization of our American medical shrines. In our restless and changing country the dwellings and haunts of our pioneer physicians disappear, and all relics and reminiscences of them become scattered or lost. Do we not owe it to them at least to collect their records while those who can recall the past are still here to help us?

Do not be alarmed! I do not intend to desecrate the post-prandial ruminative mood which sits so becomingly on your genial countenances, my learned fellows, by suggesting a subscription. All I ask is your moral support of the work of the local profession, whose duty it should be to do this work in each community. And moral support is a commodity easy to donate, even in the after-dinner glow.

For the past decade and a half, I have spent a considerable portion of my life wandering over the face of the earth seeking out and studying these memorials. They are not always easy to find. They are not usually regular objects of sightseeing, nor frequently given prominence in the guide books. Statues of generals and kings and lawyers there are, as you know, aplenty: physicians and scientists are hard to find. But there comes a peculiar satisfaction when you do find one. It is possible for mankind to remember gratefully the events that really contributed to civilization as well as battles.

For instance, I was walking a year or two ago in the majestic old eighteenth century city of Bath, around the Circus that once was and still is a fashionable crescent of residences. I had noticed a small plate affixed to one door which announced that this house was once the residence of Richard Brinsley Sheridan, so I became interested in reading these notices. Suddenly I found myself peering at a silver plate which marked the home of Caleb Hillier Parry, 1756–1822. How many visitors to that Athens of the West would know of the achievements of "the distinguished old Bath physician," as Osler called him, he who described the combination of

* Read at the St. Louis Meeting of the American College of Physicians, April 22, 1937.

exophthalmos, goiter and tachycardia; he who was the friend of Jenner, to whom the *Inquiry* is dedicated? And yet to those of us who do know the man, the thought that someone had the pride and took the trouble to point out his earthly residence, is moving and warming.

Various communities differ somewhat in their feelings towards their illustrious dead. Last year I determined to visit Berkeley in Gloucestershire, the birthplace and the scene of the labors of Edward Jenner. We established ourselves at Bath as headquarters for the trip and the word "established" bid fair to be very accurate. We were greeted on our first day with a steady, grim downpour of rain. And such wet rain—you could hardly cross the street without being drenched. We stayed in our room with a fire of channel coal (sixpence extra a day) and we stayed there for several days while the weather gave an example of what it could really do to be nasty. At last a morning of semi-sunshine gulled us into taking the bus for Bristol. A fine drizzle greeted my attempts to find the birth house of Richard Bright, and by the time we had seated ourselves in the Gloucester bus the landscape was awash again. At Berkeley it did threaten to clear and remembering the traditions of the excellent cuisine enjoyed by that convivial medical society of which Jenner was the moving spirit when it met at the Berkeley Arms, I ordered lunch and inquired the way to the local mementoes of Jenner. The landlady looked blank and asked me to repeat the name. I did so, adding the information that he had introduced vaccination against smallpox. She said she thought he was dead. I replied that I feared so, too, but would like to see his grave, or statue, or house. She said she didn't hold with vaccination herself but there was a stable boy who specialized in such matters.

While I awaited the arrival of the learned stable boy, I asked for a guide book. A pamphlet on Berkeley was procured, most of the contents of which were devoted to a description of Berkeley Castle, the seat of the Earls of Berkeley, and the principal distinction of which is that it contains a dungeon where the first Prince of Wales starved to death. There was also a brief account of Jenner, referring to his grave in the chancel of the church. The learned stable boy having arrived, would not commit himself to any definite information but ventured the remark that "Vicar would know" and conducted us to the bottom of a lane whence we could see the Church of St. Mary's and the vicarage.

As nearly as I could understand, I was told that the Vicar was away birdnesting. This was finely in the tradition of Jenner's paper on the cuckoo, but considering the weather, seemed to be carrying a tradition somewhat too far. By wandering around I suddenly came face to face with the thatched cottage where Jenner took the lymph from the hand of Sarah Nelmes to inoculate James Phipps. I recognized it from the model reproduction in Burroughs, Wellcome's exhibit at the Chicago Century of Progress Exposition, and it is well I had been there because no plaque or plate or notice indicates why this fragile structure is preserved or what happened

there. By Sherlockian cunning, we found the tomb. It is marked simply "Edward Jenner" and his dates. I liked that, but nowhere else in Berkeley is his name seen; there is not a statue or a tablet or a stone to one of the greatest Englishmen who ever lived.

We returned for lunch, but alas for the enthusiasms of biographers when they describe their hero's meals. The dining room at the Berkeley Arms was as cold as an enthusiastic New England audience. The napkins were heavy with the damp chill of mortality. The soup reminded us of the Irish famine victim's complaint about the relief kitchen, which Stokes liked to recite—"Soup, is it? Shure 'tis nothing but a quart of water biled down to a pint to make it sthronger." There was a piece of fish of the whiteness of virgin snow, which had been boiled until every vestige of animation had long since departed, and by its side with a thick white sauce, over the surface of which the congealing process of coagulation had done its deadly work. That sauce tempted me and while the waiter was out of the room I inserted my clinical thermometer into its center: I record as a solemn fact that the temperature was exactly 54 degrees Fahrenheit.

Do not mistake me. I admire the English. And the thing I admire most about them is their ability to live in England. And, furthermore, to me the greatest Englishmen who ever lived are those great and great-great-grandparents of mine who left England and settled in this land of furnaces and bathtubs, of sunshine and shad roe, of ice and mint, of cheap cigars and good coffee, and silk hats only on formal occasions.

I had a Scotch highball for dessert at the Berkeley Arms and then found there was no bus to Gloucester until morning. But no enticement would induce me to try the sheets after sampling the napkins and I hired a car from the garage (Hired? We nearly bought it) and set off. Then the heavens really opened. The vale of Gloucester may be as beautiful as the Cotswald poets say, but for me it is a vale of tears. In Gloucester Cathedral there is a figure of Jenner and a window dedicated jointly to him and his friend and biographer, John Baron.

I thought on my journey home that someone should begin an agitation for a memorial in his own home for Jenner. But then a restraining thought cooled me off. Perhaps they don't want it. One would have to approach the Vicar of St. Mary's first. Perhaps it would be better to turn the project over to an organized body—the College of Physicians and the British Medical Association.

By contrast is a visit I paid in Italy to Arezzo and asked the hotel proprietor where Francesco Redi lived. His face lit up. He took me by the arm. He said something to the cafe loungers and they accompanied us excitedly into the street. The priest joined us. I was conducted to the Via Redi and directed towards the villa. Soon I stood before two lovely old gates and passed up through the rows of cultivated plants until I stood at the entrance of a fine manor house. There a marble plate proclaimed:

Qui Nacque E Abito
Francesco Redi
Insigne Letterato E Poeta
Sommo Nella Medicina
E Nelle Scienze Naturali

One could easily imagine as one stood looking over that peaceful farm how naturally the lord of the manor would turn to those studies in insects and spontaneous generation that made him sommo in medicina et scienze naturali.

A soft voice behind me said something, and I turned to find a woman dressed, almost shabbily, in that severe black dress which Italian women affect. She had a shawl over her head and looked almost like one you used to see at Ellis Island. Yet what she said was that he was an ancestor of hers and she graciously conducted me to the chapel where all the Redis, save, apparently, Francesco himself, are buried.

I do not say that this treatment is typical of the English and Italian attitude towards their great dead, but it suggests a lesson to us.

What of the condition of our American medical shrines? I suppose there would be a very general agreement that the most important American contributions to medicine were, first, the introduction of general surgical anesthesia; second, the foundation of the physiology of gastric digestion; third, the establishment of successful ovariotomy; fourth, the suggestion of the contagiousness of puerperal fever; fifth, the discovery of replacement therapy for diabetes; and, sixth, the discovery of specific replacement therapy for primary anemia. Of equal importance as shrines of service are those institutions which have continuously, from their establishment, rendered such distinguished service to our people—our first hospitals, Pennsylvania and Bellevue, and the Surgeon-General's Library.

The South and the North share the honors of anesthesia. The Massachusetts General Hospital, as you know, keeps alive the memory of that dramatic morning of October 16, 1846. At Jefferson, Georgia, Long is represented by a granite shaft.

I have not been to Mackinac Island for many years and am indebted to Dr. Carl S. Cook of Mackinac Island and Dr. A. C. Tiffany of Mackinaw City, Michigan, for the following information:

"Alexis St. Martin was shot June 6, 1822 in the basement of what is now the Early residence at the foot of the hill leading up to this old fort. This building is still in excellent repair but gables have since been built out on the second floor. Dr. Beaumont first attended St. Martin in this basement, but immediately moved him up to the hospital at the fort. This hospital is a small one-story frame building within the fort walls. It was used as the Post Hospital until 1858 when the Surgeon's Hospital was built because of need for more room. Beaumont's hospital was then used as the

quartermaster's store until the final evacuation of the fort in 1895. From then it stood vacant until 1923 when it was rehabilitated and restored as an emergency hospital. An organization of Mackinac Island people and summer residents has equipped the old building with the necessary surgical appliances and it is now used for surgical emergencies. The present operating room is in the old part of the building, and the entire building has been refinished. The hospital is now kept up by gifts made by summer visitors. It is called Beaumont Emergency Hospital.

"There is no plaque marking Beaumont's home, but according to Meyer's book on the life of Beaumont he lived in the east quarters of the Stone Barracks, still standing.

"In 1900 a monument was erected to honor Dr. Beaumont. This was presented by the Upper Peninsula and the Michigan State Medical Societies. This monument is placed just within the Fort walls facing the Straits of Mackinac."

The inscription on the monument says, "Near this spot Dr. William Beaumont, U. S. A., made those experiments upon St. Martin which brought fame to himself and honor to American medicine. Erected by the Upper Peninsula and Michigan State Medical Societies June 10, 1900."

Our city of St. Louis here where we meet tonight, was, for many years, the home of Dr. Beaumont, but Missouri is neither the site of his birthplace nor the locale of those labors which made him famous. His birthplace in Lebanon, Connecticut, is the site of a stone shaft, dedicated on June 29, 1926.

The third spot of first rate importance as an American medical shrine is Danville, Kentucky, where Ephraim McDowell performed the first successful ovariotomy. In 1879, the Kentucky State Medical Society rescued the graves of Dr. McDowell and his wife from imminent dissolution and erected monuments over them. On this occasion Dr. Samuel D. Gross of Philadelphia delivered the oration and Dr. Lewis S. McMurtry, afterwards president of the American Medical Association, accepted the gift in the name of the Kentucky State Medical Society.

Dr. McDowell's property—his residence and office, where this classic operation was performed—was for many years badly neglected, although not because of lack of effort on the part of the Kentucky State Medical Society and other interested organizations.

Dr. Schachner, one of the biographers of McDowell, tells of visiting the house while it was a negro boarding house and as he was going upstairs the landlady pulled off a piece of lath from the disintegrating plaster wall and handed it to him as a souvenir.

Within recent years it has been possible for the McDowell Memorial Committee of the Kentucky State Medical Association to acquire this building, and when I was there last fall it was in process of repair and reconstruction. In the course of the research work necessary to secure the plans for

the restoration, the fact was uncovered that the adjoining property, which is also in good condition, was McDowell's Doctor Shop and Apothecary. The committee is trying to raise sufficient funds to purchase this property, which will cost $3,000.00, so that the entire McDowell block may be restored. For this work one of our guests at this convocation, Dr. Irvin Abell, has been so largely responsible that it is a pleasure to record our indebtedness to him.

The locale of Holmes' work on puerperal fever is indefinite. And there is no special single institution where Whipple, Minot and Murphy's work on liver in Addisonian anemia was completed. But with this, as with Toronto's honorable shrine of insulin, we can afford to wait a long time before it will be appropriate to memorialize them.

These are our proudest memories, but there are others, hardly less epochal ones. It is appropriate to my subject tonight, since Dr. Bradley is our president, to recall that in that part of Kentucky near Danville, that beautiful fertile region of the blue grass of Kentucky, there is, in Dr. Bradley's own city of Lexington, the site of the first medical college west of the Alleghenies and the fifth in the United States, Transylvania College.

The medical faculty no longer functions in Lexington, but there is a reminder of this early center of medical education still intact. Early in the nineteenth century the trustees raised a considerable sum and sent Charles Caldwell, Professor of Medicine, to Paris to purchase a library. "The time of my arrival in Paris," he wrote, "was uncommonly propitious for my purpose. The wastelayings of the French Revolution had not entirely passed away. The libraries of many wealthy persons had found their way to the shelves of the bookseller. I found and purchased at reduced prices no inconsiderable number of the choicest works of the fathers of medicine from Hippocrates to the revival of letters." These books are still in the general library building of the University—a beautiful and typical collection of an eighteenth century physician's books. They cry out for proper housing.

From this area of Western Kentucky as a center, there came the pioneer medical profession of this part of the world—of Cincinnati, St. Louis and Missouri. Since we are meeting on the very ground which was the hub of the settlement of this western territory, may I venture to recall to you some recollection of the life and experience of our pioneer Missouri physicians?

I have here in my hand a little book, one of the rarest examples of Americana, which is entitled SAPPINGTON ON FEVERS. It was printed at Arrow Rock, Missouri, in 1844.

Those of you (naturally I address particularly the Missouri part of our audience) who have visited Arrow Rock, which is about midway between St. Louis and Kansas City in a beautiful rolling countryside reminiscent of the blue grass region of Kentucky, will remember the old Arrow Rock

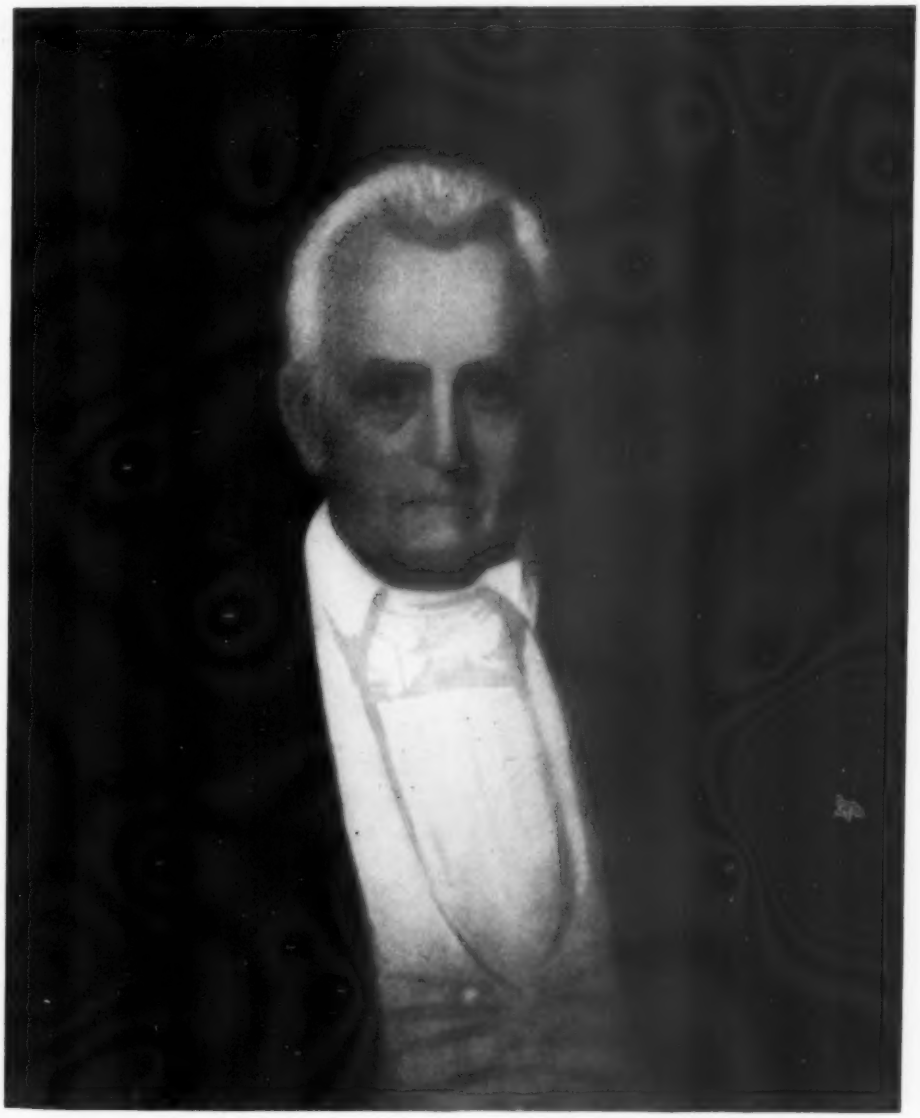

FIG. 1. John Sappington. From the portrait by George Caleb Bingham.

Tavern which was close to the home of John Sappington, and which now exhibits a museum of his case books, saddle bags and other relics.

John Sappington was born in Maryland in 1776. His father joined the tide of western emigration and moved to Tennessee, settling in Nashville. John Sappington studied with his father as preceptor and later was associated with him in practice in Nashville. In 1814 he rode to Philadelphia on horseback, where he attended for one year, from 1814 to 1815, a course of medical lectures and received a diploma from the University of Penn-

sylvania. He heard the arguments for and against the violently depletive treatments that the followers of Rush and Cullen taught and practiced in the treatment of fevers. Returning to Tennessee, he emigrated in 1817 to Missouri and located in what was then the western frontier settlement of Howard County. Two years later he moved across the river and settled in Saline County, near Arrow Rock.

The medical problems of this territory were quite as grave as any other danger to which the settlers were exposed. There was a well defined sickly season, starting in July and extending into September until the first frost. Fever and chills were nearly universal visitations and the farmers expected so much incapacitation at this time that they made particular efforts to have their crops and other important matters attended to before the onset of the sickly season.


FIG. 2. The Tavern at Arrow Rock, Missouri. It houses many Sappington relics.

The cause of these fevers and agues was unknown. Daniel Drake writing in 1830, says " There is a noxious gas given out throughout the great Mississippi Valley system which affects the people of the west and south." This noxious gas theory is the one which gave malaria (mal air) its name. Drake afterwards discarded this noxious gas theory.

In Morse's " Western Gazeteer " in 1810, in regard to Louisville, Kentucky, it is said that " its unhealthiness due to stagnating waters back of the town has considerably retarded its growth."

Early settlements in Howard and Saline Counties, Missouri, were frequently abandoned due to the prevalence of shaking agues.

It is to the credit of Dr. John Sappington, and it is the merit which has given his book permanent value, that he early recognized the specific therapeutic nature of quinine in these autumnal Valley fevers. Let me emphasize that it was quinine on which he relied. Daniel Drake preferred, in many cases, Peruvian bark to quinine but Sappington wrote: "The names of Pelletier and Caventou, who first separated the pure alkaline salt, called quinine, from the bulky and inert mass in which nature had placed it, deserve to be remembered with gratitude by all mankind."

In this particular community, contiguous to our meeting place tonight, Sappington's influence was very strong. It is not too much to say that his advocacy, in season and out, of the virtues of quinine did much to make this section a healthy place of residence.

FIG. 3. Dr. Sappington's grave in the family cemetery at Arrow Rock. In this same cemetery are buried two governors of Missouri, C. F. Jackson and M. Marmaduke.

He had by no means an easy time of it. His few professional brethren had been strongly imbued with the virtues of the depleting system of Rush, under whom many of them had sat. He probably shared, as Dr. Thomas B. Hall suggests, Oliver Wendell Holmes' opinion of Rush's epigram, "Medicine is my wife and Science my mistress," of which Holmes said, "I do not think that the breach of the Seventh Commandment can be shown to have been of advantage to the legitimate owner of his affection."

Even so fair minded an inquirer as Dr. Daniel Drake was unimpressed by Sappington's ideas. Drake was a great influence all over the Mississippi Valley in those early days.

His "Western Journal of the Medical and Physical Sciences" was a source of light and comfort to physicians all over the West. At a time when the companionship and advice of fellow physicians was keenly missed on account of the sparsely settled land, the pioneer physician found in this journal both accounts of medical progress in the great centers of the world and also accounts of the local diseases of his own territory—new, strange and largely unrecorded in textbooks.

These accounts came largely from the pen of Drake himself and were the basis for his really major contribution to medical science—his "Prin-

THE

# THEORY AND TREATMENT

OF

# FEVERS,

BY

DR. JOHN SAPPINGTON,

SALINE COUNTY, MISSOURI.

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REVISED AND CORRECTED

BY FERDINANDO STITH, M.D.,

FRANKLIN, TENNESSEE.

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A Paul may plant, an Apollos may water, but the increase is of God.—*First Epist. Paul to the Cor., Chap. 3d, 6th verse.*

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ARROW ROCK:

PUBLISHED BY THE AUTHOR.

1844.

FIG. 4. Title page of Sappington on Fevers.

cipal Diseases of the Internal Valley of North America" (1850). To collect material for this, Drake traveled restlessly up and down all our river valleys. He visited Arrow Rock, Missouri, some time about 1835–1840, probably because he had heard of the fame of Dr. John Sappington and his treatment of autumnal fevers. Sappington condemned the depleting treatment of purging, vomiting and bleeding, because all that is necessary to effect a cure is quinine, "one grain every two hours, day and night."

Drake records (p. 170, Interior Valley) a visit to Arrow Rock and a conversation with Dr. Price, who was Dr. John Sappington's son-in-law.

# DR. JOHN SAPPINGTON'S
# ANTI-FEVER PILLS.

## DESCRIPTION AND TREATMENT OF INTERMITTENT, OR AGUE AND FEVER AND BILIOUS FEVER, AND ALSO DIRECTIONS FOR PREVENTING THEIR INCEPTION AND RETURN.

### 1st.—OF INTERMITTENT, OR AGUE AND FEVER.

I consider all fevers of an intermittent character which cool off once in twenty-four hours, whether preceded by a chill or not, or whether the chill and fever rise and continue together, or if there be no chill at all. Sometimes fevers of this character continue twenty-four or forty-eight hours without an intermission, and sometimes it occurs every third day only. Nine-tenths of the fevers of this State, and most other States of this Union, partake more or less of this character; and in all their various appearances the treatment should be the same.

**TREATMENT.**—If the patient prefers taking a puke or purge before he commences the use of this medicine, I have no objection, but it is rarely if ever necessary. A grown person will take for a dose a pill or common sized teaspoonful of the liquid* every two hours, both night and day, until the disease is broken, (always observing to shake the liquid before used,) and children will use less in proportion to age; for instance, a child eight or ten years old will take thirty or forty drops, one of three or four years old will take fifteen or twenty drops, and infants three or four weeks old will take from three to six drops, and repeat and continue as recommended for grown persons. Should the bowels be too costive, or in other words, not purge once in thirty-six or forty-eight hours, give broken doses of salts, or oil, or injections, and should they purge oftener than twice in twenty-four hours, give six or eight drops of laudanum two, three or four times a day until the looseness is restrained. Diet to be such as is suitable for a sick person; drink cold water.

### 2d.- BILIOUS FEVER.

This is a more obstinate and dangerous disease than intermittent, or ague and fever, there are generally three or four days of indisposition previous to the development of fever; and generally chilly sensations for a day or two after.

When this disease is properly formed, it rarely yields to any treatment under eight or ten days, and sometimes a much longer time.

**TREATMENT.**—In the first stage of the disease, I give a puke or one or two small doses of calomel or some other medicine that will operate upon the stomach and bowels; under any circumstances I object to giving more strong medicine; and am decidedly of opinion that a frequent repetition of them does more harm than good. After thus operating on the stomach and bowels and even without it, if the patient has become weak from the duration of disease, I commence with the pills or drops and give a dose every two or three hours, with Virginia snake root or some other sweating tea, such as hyssop, sage, or balm. Should the patient suffer much pain in the head, back, or elsewhere, give twenty or twenty-five drops of laudanum at night; children should take less, corresponding to their ages. Should the patient become debilitated from a continuation of the disease, and particularly if the hands and feet become cold, give a portion of toddy or wine every three or four hours, continuing all the time the use of the pills or drops until the disease is broken. I would prefer the bowels to be in rather a costive than laxative condition, but should they become too inactive give oil, or broken doses of salts and injections, or if they become too loose, give six or eight drops of laudanum, two, three or four times a day, until the looseness is restrained. Diet should be light, and taken often, but in small portions at a time; drink cold water.

### 3d.—OF PREVENTING THE INCEPTION & RETURN OF AGUE AND BILIOUS FEVERS.

The remedy I recommend for the cure of these diseases, will prevent their formation if taken in time. If used as a PREVENTIVE, a person should take three or four doses a day for seven or eight days in succession, then discontinue it for ten or twelve days, when it will be again used as above directed, and so on until the sickly season has passed by; persons residing in unhealthy situations, or travelling through sickly districts of country, will find the PREVENTIVE plan greatly to their advantage. To prevent relapses of ague and bilious fever, an individual would do well to take three or four doses of the medicine a day until his strength and complexion are restored, particularly if he has had several relapses already.

The reader will find a considerable change made in these, when compared with former directions; this has been produced from the fact that my WORK ON FEVERS is now in general circulation, and that almost every one can get a book who desires further information on these or other fevers on which it treats. Moreover, Physicians, Druggists, Apothecaries, and many other individuals, are now making and offering to the public, pills purporting to be of the same materials and quality of mine, and which in many instances, no doubt, are greatly weakened as well as adulterated; and believing that in this manner frauds will be ingeniously practiced, I have caused a fac simile of my signature to be pasted around each box, and these new directions will now accompany the genuine Sappington Anti-Fever Pills, instead of being tied around them as heretofore.

These Pills I can recommend as being equal and similar in every respect to the pills formerly sent out by me, and that persons can avoid imposition by buying THESE pills instead of other pills of DOUBTFUL strength and purity.

As the community as well as the profession are partial to acting on the stomach and bowels with some purgative medicine, and as I have admitted in my Treatise on Fevers that it is generally proper, and sometimes essentially necessary that some purgative medicine should be taken by the patient before he commences the use of my Anti-Fever Pills; to remove any indigestible or bad accumulation from the stomach and bowels, Dr. Wm. Price, of Arrow Rock, Mo., my son-in-law, has prepared what he conceives to be a suitable purgative for that purpose, to accompany the Anti-Fever Pills; and I am much inclined to the opinion that he can prepare as good a medicine of the kind as any other person—by my advice, however—to be taken as often only, and under such circumstances as is recommended in my Treatise on Fevers, or as is advised in the directions around my Anti-Fever Pills.

*For grown persons or children, who prefer taking medicine in a liquid form, it can readily be prepared by any one in the following manner, viz: pound twelve pills well, put the preparation into a vial, and add two common sized tablespoonfuls of water or whisky to it, spirits are best, and it matters but little what kind of spirits are used. Any quantity of the liquid may be thus prepared by increasing or diminishing in a just proportion the quantity of ingredients above mentioned.

JOHN SAPPINGTON, Saline Co., Mo.

January, 1848.

**Price One Dollar per Box.**

FIG. 5. Advertisement of Sappington's pills.

He probably met Sappington, but apparently they conceived no high opinion of each other. Drake learned nothing from Sappington's advocacy of the specificity of quinine. He recommends, under treatment of autumnal fever (p. 782) catharsis with calomel and emesis with tartarized antimony, and bleeding. This prepared the patient " for the reception of the bark and other tonics." Quinine he regarded as a tonic only. His conception of the problem was far inferior to that of Sappington, the backwoods general practitioner, whose mind went straight through to the conception of the specific action of the drug.

A recorded experience from a physician's own lips of the classic form of treatment is that from Dr. James C. Finley who, in a medical periodical in 1830, told of his own experiences. By his own direction he was violently purged and had an emetic-cathartic administered. This treatment was continued for six days when " Dr. Childers, a physician of great observation and experience, who very kindly attended him during the remainder of his illness considered him to be out of danger and prescribed the Sulphate of Quinine." He said his system was completely prostrated by the end of the third day. He became delirious, which was attributed to the action of the quinine and the drug was discontinued. After that he became comatose and all hope for his recovery was abandoned. When he did recover consciousness " the mind as well as the body long remained in a state of infantile weakness."

In the first chapter of his treatise, Dr. Sappington gives " The author's reasons why he has departed from the practice of the old school physicians and all others in the treatment and cures of fevers." He states his disapproval of the teachings of Rush and Cullen " which was chiefly that of bleeding and acting on the stomach and bowels with emetics and cathartics as long as they thought the patient could stand them." He suggests that quinine is a tonic and not a stimulant and " is not injurious when taken in the hot stage of fevers as has been frequently said of it."

He carried this idea over into the treatment of yellow fever in which the depleting system must have been particularly exhausting, added to the natural depleting effect of the disease.

Slowly his ideas gained ground and he won converts among his professional colleagues. One physician, Dr. W. H. Shelton, was led to throw aside the teachings of Rush and to use Sappington's pills as directed and marvelled that he was able to cure three hundred cases of fever without once resorting to the lancet.

A typical experience was that of Dr. George Penn, a graduate of Jefferson Medical College, who came to Saline County in 1826, riding all the way on horseback. He formed a friendship, and afterwards a partnership, with Dr. Sappington. Let me record one of his experiences as retold by Dr. Thomas B. Hall:

" John bringing a sack of corn with him to the mill reaches Jonesboro at 4 p.m., on a crisp, clear December day. He leaves word for the doctor, who is out, to be sure to come that night to see his sister.

" Dr. Penn, returning home from his rounds, already having ridden fifteen miles in his visits to the sick, receives the message and after eating his supper, prepares for the trip. All his practice is done by riding, the roads making any other means of transportation out of the question. In his stable are two horses and a mule. This latter animal being recently introduced to Missouri by the Santa Fe traders, from Spanish settlements around Santa Fe.

" This is how we acquired our famous Missouri mule, and although it is hard to believe, some were esteemed for their good riding qualities, in addition to their recognized endurance. The mule and a large white horse bear the doctor during his day travels, but by night he rides a small sure-footed sorrel, which his Negro servant now brings for him to mount. His servant properly fastens the saddle bags to the saddle. The Doctor with his pipe lighted by an ember from the hearth, places a large calibre, loaded, flint lock pistol in a holster, which he straps around his waist, mounts his horse and is off on his long trip. Crossing Salt Fork, he soon leaves the skirt of timber and is on the prairie, where the narrow trail leads through prairie grass which extends as high as his horse's head. Now and then he comes to an open place where the grass has been burnt off. Fording Blackwater, he rides from a timbered section to the prairie again and within one and one half hours from the time he has left his home, reaches the two-room log cabin of Finley, in a timbered strip near Heath Creek.

" Entering the large room of the cabin, which is lighted by a blazing fire in the large fireplace, he is greeted by Finley and his wife and the least bashful of their seven children. The room is scantily furnished, with home made furniture, in one corner is a spinning wheel, in another three long heavy flint-lock hunting rifles and a smooth bore flint-lock musket. In front of the fireplace, the two older boys are running bullets and cutting round patches from the buckskin for the rifles. The atmosphere is still full of the odors of the evening meal, cooked in the open fireplace.

" The father takes, from the mantle, a shallow open iron pan, which is filled with melted grease and has a neck out of which protrudes a wick made of tow. Lighting the wick from the hearth, he brings this crude light for the doctor to examine his daughter, aged five, who lies apathetically, covered with a buffalo robe, in a trundle bed in one corner of the room.

" An examination quickly confirms the doctor's preformed opinion of the case, for he had prescribed much quinine for the Finley family during the months of August and September and he remembered that Mrs. Finley had told him at the camp meeting on Salt Fork that it was a constant battle to force the bitter quinine down her little daughter and that she frequently became nauseated and vomited.

" A recurrence of the ague was to be expected and the child's large spleen settled the diagnosis. Drawing the hickory stool on which he is seated near the fireplace so as to have a better light and more warmth, he seats himself and places his saddle bags across his knees, one on either side, the

broad leather band connecting the bags, in this way making him a work bench across his knees. In one compartment of his bags are two, 3-ounce bottles, one containing quinine sulphate and the other calomel. He asks the father for a cupful of whiskey, which is quickly obtained from the two-gallon jug in one corner of the room. Fortunately the family has a four ounce bottle which has a cork. This is filled with the whiskey and held near the doctor, who has the bottle of quinine on the large leather band passing over his knees, thrusts a knife with a long narrow blade which he carries with him for this particular use, into the open quinine bottle. His practiced eye can tell to $\frac{1}{10}$ of a grain, the amount of quinine sulphate necessary to make two or four grains when balanced on the point of the knife. Measuring in four grain doses and counting carefully the knife eight times dumps its load in the four ounces of whiskey. This gives him a dosage of one grain to the dram and he has found it the best way to give quinine to infants and children. A few drops from a vial labeled 'Elixir of Vitrol' are added to the four ounce bottle to increase the solubility of the quinine.

"Two teaspoonfuls of this medicine are administered to the child with instructions to give thereafter, one teaspoonful every three hours night and day. When about to leave, Mr. Finley states that he has no money to pay him, but offers to pay his bill with two sacks of meal worth about 75c a sack. This the doctor assents to and instructs him to leave the meal at the mill at Jonesboro, where he already has a good many bushels to his credit for his professional services to other patients.

"This he expects to sell for good Spanish coin to the Santa Fe traders the next spring. Mounting his horse, he starts home by the same trail."

The amount of quinine Dr. Sappington used is an index of the thoroughness with which this countryside was de-plasmodiumed. John Farr of Philadelphia was the first chemist in America to manufacture quinine. He expressed great surprise at Dr. Sappington's orders of 500 pounds at a time. Indeed, Mr. Thomas Hart Benton tells me that it was a legend in his home that the reason Dr. Sappington first advocated quinine was that he ordered a hundred ounces and by mistake received a hundred pounds. He had a supply to be got rid of and he was a practical man. But then, as everyone knows who has seen Mr. Benton's murals, he has a somewhat mordant sense of humor.

Other diseases in this country unfamiliar to us, the successors of the pioneer physicians, were Asiatic Cholera and Typhus and "Black Leg," which was scurvy, so called on account of the petechial hemorrhages on the skin of the legs.

Dr. Sappington's drugs which he carried in his saddle bags were, besides quinine, opium in the form of powder, laudanum and paregoric, mercury, iron, oil of chenopodium, digitalis, arsenic in the form of Fowler's solution. He performed many vaccinations, carrying the lymph on bone points. He had no hypodermic syringe but allayed pain by injecting a small enema of sweet milk containing 30 to 60 drops of laudanum. He practiced counter-irritation by the free use of mustard plasters and Spanish fly ointment.

Dr. Sappington's popular reputation today among those who have heard of him rather vaguely is that he was an irregular practitioner, an advertiser and almost a quack. This is partially, but not entirely, deserved. He was so passionately convinced of the truth of his cause—that the way to make the countryside healthy was to distribute quinine generally—that he felt any means justified the end. He sold his fever specific to the public. They were widely known as Sappington's Anti-Fever Pills. He excused this conduct on the grounds that there was a tremendous prejudice against quinine and if he had sold them as quinine they would not have been used, whereas he could introduce them as Anti-Fever Pills. He sold his book to the laity and wanted to get it into their hands because he realized that the profession did not accept his view: perhaps they were too educated: and it must be remembered that personal reminders of his existence to the extent of professional cards in the paper was the country practitioner's common practice.

It was his habit on his rounds to scatter blue grass seed over the fields by the side of the road and to try to make Missouri resemble in verdure, Kentucky.

The story of the desecration of his grave has been frequently garbled. The actual facts, however, need no retouching. He had a dread of being buried underground, and he had a lead coffin constructed, which he kept under his bed—usually filled with apples. He died in 1854 and was duly interred in the lead coffin above ground, as directed. When the Civil War came along, the Confederates ran short of ammunition and someone called attention to the magnificent supply of lead exposed at Arrow Rock. So they were ordered to take as much lead out of the doctor's coffin as they wanted and in doing so mutilated it considerably so that, as I understand, the skull was exposed for a time. William Harvey, it will be recalled, was also "lapt in lead."

This John Sappington is the sort of figure whose memory should be preserved by us. Everywhere in the United States there are materials for the record of a complete history of medical practice there. In only a few instances have they been utilized. I have been made very enthusiastic by the publication of such works as the histories of medicine in San Antonio, Texas and Sullivan County, Indiana, lately published. This is far more appropriate work for the American medical historian than delving into incunabula or Babylonian mysteries.

This is neither the time nor the place for any specific recommendations. But I hope you will not think it presumptuous of me to suggest that it is one of the legitimate functions of this College to encourage and to aid the preservation of the memories of the figures and the landmarks of our glorious past.

*Note:* It is a pleasure for me to acknowledge my indebtedness in the preparation of this paper to Dr. Thomas B. Hall of Kansas City. I have utilized not only the results of his scholarly researches into the history of Dr. Sappington, but often his very words. See "John Sappington, M.D." by Thomas B. Hall, M.D., Missouri Historical Review, January, 1930.

*AN ARTICLE CONTRIBUTED TO AN ANNIVERSARY VOLUME IN HONOR OF DOCTOR JOSEPH HERSEY PRATT*

# THE RELATION OF PULMONARY FUNCTION TO FIBROSIS AND EMPHYSEMA *

By JAMES ALEXANDER MILLER, M.D., F.A.C.P., and ISRAEL RAPPAPORT, M.D., *New York, N. Y.*

IN a recent publication [1] we presented a preliminary communication suggesting our ideas of intrinsic lung function. At that time we reached the following conclusions:

(1) The intrinsic function of the lungs consists in their alveolo-capillary surface-creating and self-cleansing power.

(2) Disturbance in these functions manifests itself by obliteration of some and compensatory hyperfunction of other lung areas.

(3) In pulmonary fibrosis there is a permanent loss of functioning lung units, due to failure of the intrinsic self-cleansing function, and in emphysema there occurs an irreversible loss of retraction power in the compensating lung units where the operation of the intrinsic function of creation of new breathing surface fails and the available spaces are merely overstretched by the operation of extrinsic breathing.

It is our present purpose to further elaborate and elucidate the ideas previously suggested.

## THE PREVAILING CONCEPT OF LUNG FUNCTION

The prevailing ideas concerning lung function and the nature of pulmonary fibrosis and emphysema may be briefly summarized as follows. The respiratory system of air passages and pulmonary alveoli serves the purpose of ventilation. In this function the myoelastic elements of the airpassage system play the rôle of an active force in the expiratory retraction of the lung. The main activity producing ventilation is, however, the activity of the neuromuscular apparatus of breathing in the chest wall and diaphragm. The lungs act as a mere air reservoir, and the chief purpose of the lungs is to afford the breathing surface necessary for gas exchange. The structures constituting the breathing surface play a merely passive rôle. According to these ideas pulmonary gas exchange is determined essentially by cardio-circulatory function which regulates the extent of blood circulation in the lungs. Circulation and ventilation are recognized to be closely correlated to meet changing conditions, as for example from rest to exercise. It is believed that to increase gas exchange in the lungs all that is needed is to increase the work of the heart to drive more blood through the lungs,

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and to increase the work of the breathing apparatus, that is, the chest wall and diaphragm, so as to maintain adequate ventilation of the air reservoir in the lungs.

According to this concept the lung, as compared with other internal organs of the body such as the kidneys, the liver, etc., has, strictly speaking, no definite function of its own. This concept was recently well expressed by Y. Henderson [2] as follows:

> The lungs are peculiar organs in that they have little independent activity or self-regulation. Their activity is mainly determined and controlled by influences outside the lungs themselves. . . . In their abnormal physiology the dominant influences are generally not developed in the lungs themselves, they are induced by conditions in other parts of the body.

It naturally follows that the prevailing ideas of the nature and pathogenesis of pulmonary fibrosis and emphysema are based upon the concepts of the lung and its limited function. Accordingly, pulmonary fibrosis is considered a purely structural process consisting of obliteration of the air-spaces by connective tissue the formation of which is elicited by inflammatory products or foreign matter deposits. This fibrous obliteration of the air-spaces interferes with the efficiency of the ventilatory bellows' action since it reduces the distensibility and retractility of the lung tissue. As the fibrotic process becomes more extensive, the resulting loss of reserve air-space becomes a functional handicap.

Emphysema also is looked upon as essentially a purely structural process consisting of a loss of elasticity and retractility of the tissues of the lungs of various etiology, much of which is still obscure. Here again it is held that these structural changes interfere with the efficiency of the ventilatory bellows' action and result in over expansion of the lungs because of the force of the breathing apparatus.

The prevailing, just outlined concepts about the nature and pathogenesis of pulmonary fibrosis and emphysema have been well expressed in the recent publications of McCann,[3] Christie,[4] Meakins and Christie,[5] Kountz and Alexander.[6]

Clinical experience has, however, forced upon us the consciousness that there are many functional disturbances associated with these structural changes. Among others Knipping et al.,[7] Richards and Cournand,[8] have made extensive studies of these functional disturbances. However, these studies concerned themselves mainly with the disturbances of circulation and ventilation which affect gas exchange and which are considered as sequelae of the structural changes above noted. When these functions of circulation and ventilation fail, the eventual outcome is thought to be cardiac failure.

It is, therefore, obvious that in these prevailing concepts there is no suggestion that pulmonary fibrosis and emphysema might represent primary disturbances in the function of the lungs with a specific function of their

own, nor is there any suggestion that the functional failure which results from these conditions might represent organ failure of the lungs in the strict sense of that term.

## Our Concept of Lung Function

We postulate the existence of a special organ function in the lungs, analogous in every sense to the special functions of the other organs of the body. Studies of the situation existing in other organs show that the special function of each organ invariably consists in special adaptations of the structure of the units of that organ to some particular physicochemical process involved in its function. In every case the main purpose is to serve the exchange of certain substances between the blood and the specific cells of each organ. This may be either absorption into the blood of substances necessary for the life activities of these cells, or, on the other hand, the elimination of the waste products of cellular activity. The physicochemical processes involved consist chiefly of filtration of fluid and the diffusion and absorption of gases and solutes. The structure of each organ is adapted to perform its particular function.

Each organ consists of a vast number of individual units each one of which is endowed with far-reaching independence for function and also a great capacity for compensatory hyperfunction in case of failure of other units of the organ. The organ as a whole is active only in the case of an increased demand for function, and at rest only a fraction of the units are simultaneously at work. Barcroft [9] recently described this situation for the case of the lungs as follows:

> The lungs are not built for the animal as it stands or lies, they are built to subserve the needs of the animal when it is putting forth the utmost exertion of which it is capable.

Alternation of these fractions of the available organ units is the rule during rest. The structural adaptations characteristic of the organ units are linked up with the functional circulation and filtration processes, and together with the circulatory motor force behind these they form a functional mechanism which is adjusted to the pressure conditions prevailing in the circulation. This functional mechanism the motor force of which is the cardio-circulatory pump, is correlated with, and counterbalanced by, a parallel functional mechanism by virtue of which the structures of the organ units execute certain movements of adaptation under the effect of the pressures which prevail in their environment, or the effect of the tensions or active contractions inherent in their own tissues, which thus serves as another motor force behind their intrinsic functional mechanism. This is true of the kidneys, of the glands and many other organs, and we suggest that the same mechanism operates in the lungs.

## Structural and Functional Organization in the Lungs

The characteristic structural units of the lungs are the air-spaces. As in the other organs we conceive that these units are endowed with far-reaching independence of action and great capacity for compensation one for another. These units function in alternation at rest, and this alternation is associated with shifts from the functional (pulmonary) to the nutritional (bronchial) circulation. The functional circulation is provided for by an exceptionally large capillary network, and there is an exceptionally abundant filtration of fluid from these capillaries into the air-spaces. We conceive that the intrinsic unit function in the lungs is served by a double motor mechanism the forces of which are acting in opposite directions, namely, the erectile force of the functional circulation which acts in a centripetal direction toward the lumen of the air-spaces, and, on the other hand, the air-space expanding force which acts in a centrifugal direction from the center of the air-spaces.

The specific physicochemical processes of gas exchange and evaporation require exposure of the circulating blood over the greatest possible surface which is constituted of a tissue membrane of extraordinary delicacy. We conceive, therefore, that it is the intrinsic function of the units of the lungs to adapt their structures so as to create such a surface, to maintain it constantly, and to regulate it under all circumstances in accordance with the requirements of the body for gas exchange and for evaporation in the lungs.

Thus, we have reached the conclusion that the creation, maintenance and regulation of internal surface adequate in quantity and quality for the momentary requirements of gas exchange and fluid elimination under all conditions is the intrinsic function of the lungs.

In our studies of this subject we have found that creation by function was implied already in Huntington's [10] "selective theory" of phylogenesis of the lungs. The concept could not have been better expressed than by the statement: "A man is really not winded but lunged," included in this brilliant essay. The outstanding studies of Heiss [11] on the embryology of the lungs have demonstrated that creation of an ever greater internal surface is the basic biologic principle of development of the lungs both before and after birth.

*A. Antenatal Development of the Lungs.* Embryologic development of the lungs takes place by biological growth of its primitive anlage consisting of an entodermal and a mesodermal component. Growth of the former results in an increase of the mass and size of the organ. As the remarkable studies of Marcus [12] have shown, growth of the mesodermal component increases the complexity of septal partitioning into new units of the organ. Wherever surface is to be greatly increased Nature resorts to such an infinite subdivisioning of available space. Antenatal lung development consisting of the centrifugal sprouting of the entodermal and the centripetal partitioning of the mesodermal component of the lung anlage, serves thus

the creation of a great number of organ units with a vast potential internal surface.

*B. Establishment of Pulmonary Function at Birth.* By the recent outstanding work of Broman,[13] Willson,[14] Bremer [15] our modern concepts of the functional development of the lung have become well established. This work has particularly served to confirm the concept that the first air-spaces of the lungs are produced by the mechanical disruption of the continuity of the entodermal lining of the lung units. Establishment at birth of two functional mechanisms acting in intrinsic lung function brings about the opening of the lungs' air-spaces and the creation of the breathing surface. The motor forces behind these two mechanisms are (*a*) centrifugal thoracic traction, as maintained by the permanent tonic activity of the neuromuscular apparatus of breathing (chest wall, diaphragm and bronchi), and (*b*) the centripetal erection of the pulmonary capillaries, as maintained by the pumping action of the heart. At birth these two mechanisms act together to disrupt the continuity of the entodermal covering of the lung units, to expand these into air-spaces and to expose the vast capillary surface of the lungs within the lumina of the air-spaces, which thus become separated from the outside air only by an extremely delicate membrane of the mesenchyme which is the carrier of the vascular system everywhere in the body. Disruption of the entodermal continuity is prepared for by prenatal degeneration and loosening of the lining of the terminal buds. Capillary erection is accomplished by marked increase in the pulmonary circulation as the ductus Botalli is kinked off and all blood begins to pass through the lungs. In the air-spaces thus created at birth there is established a permanent air depot (residual air) of the lungs since only a part of the air-spaces which are formed are allowed to retract at one time as function continues in alternating groups of units.

At the same time and in the same manner there is established in the lungs a permanent blood depot, that is, the large amount of blood which is rushed into the organ is transmitted to the systemic circuit only in fractions governed by the subsequent periodic rhythms of the heart and in proportion to the venous return.

It is our conception that once thus set in motion the just described functional mechanisms continue their uninterrupted course throughout life, with intrinsic lung function continuing to consist of air-space expansion and breathing surface creation by disruption of the entodermal continuity of the air-spaces and the pushing forward of the capillaries into their lumina.

*C. Postnatal Development by Combined Growth and Function.* Evidence of continued biological growth of the lungs after birth was brought forth, in addition to that already mentioned,[13, 14, 15] by the work of Bender,[16] Hilber,[17] Tiemann.[18] With the more recent work of Bremer [19] continued development of the lung throughout at least the upgrade period of life stands now conclusively proved. During the first years of life there is great

demand for additional breathing surface and air-space, which is met at first by the growth of additional new lung units. As the child grows and the intrinsic function of the lungs increases in efficiency and power, demands for increased function are being met more and more by increased function of the already available units. For a number of years, varying in each individual, there continues after birth the development of the lungs by increase of both growth and function. The principle underlying both these factors, growth and function, is internal surface enlargement by means of increased partitioning.

*D. Permanent Lung Function: Structural Adaptation for Intrinsic Unit Function.* (*a*) *Adaptations of the membrane which serves as the breathing surface.* Haldane and his associates recognized the fact that there must be some innate lung function other than that of a simple ventilatory process. They suggested that this consisted in gas secretion by the capillary endothelial membrane which separates the blood from the air-spaces. Haldane and Priestley [20] say:

> The tissue elements in which oxygen secretion occurs might either be the alveolar epithelium, the capillary endothelium, or both. . . . It seems, on the whole, more probable that the secretory activity is localized in the endothelial cells of the capillaries since they are in direct contact with the blood.

No evidence of such secretion has ever been forthcoming. But there has been a considerable amount of new knowledge recently accumulated in the pioneer work of Landis [21] and that of Peters [22] concerning the nature of the activity of the capillary endothelial membrane in the tissues of the body in general and in the special organs in particular. We now know that it is the function of this membrane to regulate its permeability in accordance with the type of capillary filtration required for the nutrition or function of the tissue or organ in question. This is now designated as the "blood-tissue barrier" function in which the endothelial membrane of the capillaries operates in association with the mesenchyme matrix which intervenes between every cell of the body and its particular capillary. The paramount physiologic rôle played by the uninterrupted stream of tissue fluid, which maintains the mesenchyme matrix in a semifluid state, has been particularly emphasized by Schade [23] and Beneke.[24] There is evidence that capillary permeability implies transitory changes in the consistency of the endothelial membrane.

A recent publication of Field and Drinker [25] contains the following statement bearing upon the semifluid consistency of the mesenchyme matrix:

> It seems apparent that these passages of particles through intact capillary membranes resemble the passage of a globule of mercury through a gelatin film, a migration which leaves no trace of damage. One sees the same sort of things on passing a needle through a bit of gelatin. Again no trace remains and at all times the gelatin has retained its integrity as a membrane.

In what is perhaps the most brilliant histophysiological study yet made on the living capillary wall Clark and Clark [26] very recently drew the following final conclusions:

The present observations have shown that the consistency of the blood vascular endothelium is characterized by extreme lability. The rapidity with which changes in endothelial consistency may take place, and the relatively minute stimuli necessary to elicit certain of these changes, together with their reversibility, are of unquestionable physiological importance and should be taken into account in any comprehensive consideration of the morphology and physiology of blood vascular endothelium.

As the consistency of the endothelial membrane softens, fluid escapes from the capillaries. The mesenchyme matrix which transmits this fluid is also of semifluid consistency in most tissues of the body but much more so

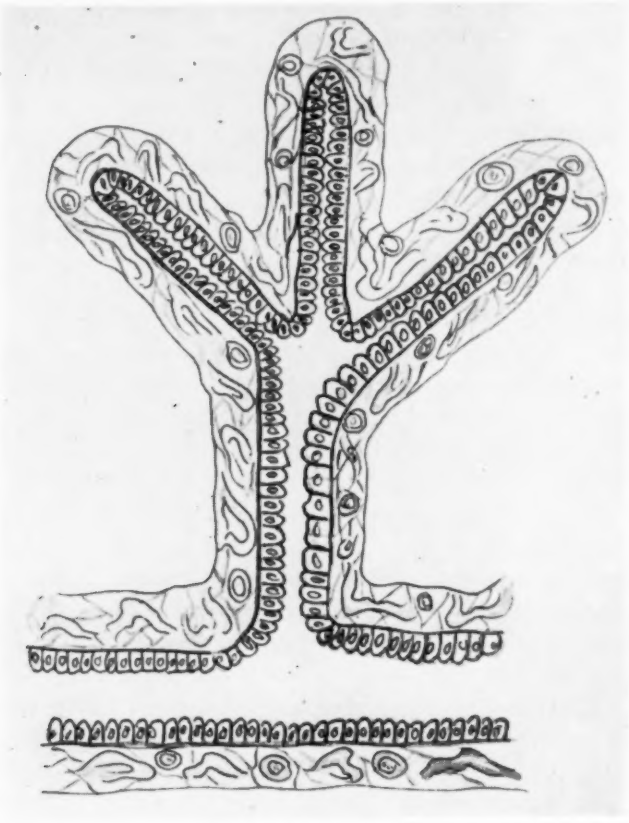

FIG. 1. Prenatal unit.

in some than in others. If we consider the extraordinary and constant mobility of the lungs, and the vast fluid filtration which, as shown by the studies of Terry,[27] Swindle,[28] constantly pours out from the capillaries of the air-spaces, it seems logical to assume that the consistency of the mesenchyme matrix in the lungs must be capable of unusual changes. In the lungs, gas exchange is the reverse of that in all other tissues of the body, as here oxygen diffuses into and carbon dioxide diffuses out of the blood. With this reversed gas exchange process there is closely linked a physico-

chemical process which must play a rôle in the unusual and characteristic consistency changes which make possible the histostructural changes which underlie intrinsic unit function. In our conception of intrinsic lung function we postulate definite consistency changes in the mesenchyme matrix as well as in the endothelial membrane of the lungs' capillaries as a part of the

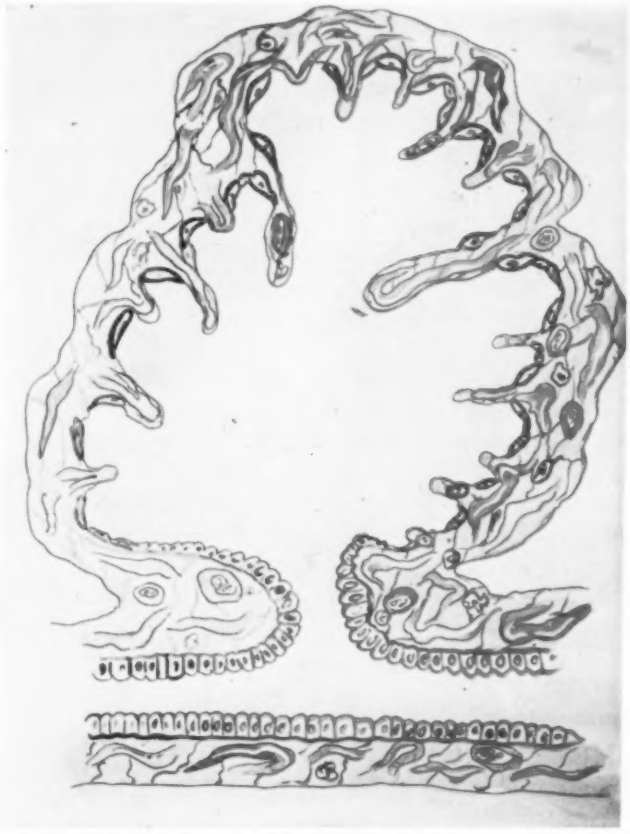

FIG. 2. Unfolding and partitioning with establishment of respiration.

structural adaptation of the organ to its particular function. We suggest that these changes in consistency in the endothelial membrane and in the semifluid mesenchyme matrix of the lungs are correlated with the functional mechanisms which act in intrinsic function. Thus, centrifugal thoracic traction acting upon the softened structures of the units operates as the air-space expanding force, while the centripetal erectile force in the capillaries is allowed to press forward within the softened and thinned-out mesenchyme layer. The springing-forward into the lumen of the air-spaces of these capillaries constitutes breathing surface creation.

The drawings here attached represent an attempt at schematic illustration of our concept of breathing surface creation in intrinsic unit func-

tion. We are showing the lung unit in the prenatal state (figure 1), its subsequent unfolding and partitioning with establishment of respiration at birth (figure 2), and finally the alternation of resting and functioning units as indicated by the great differences in breathing surface made available by simultaneous opening as well as subdivisioning of the unit by the great number of mesenchymal partitions carrying the capillaries into the lumina of the air-spaces (figure 3).

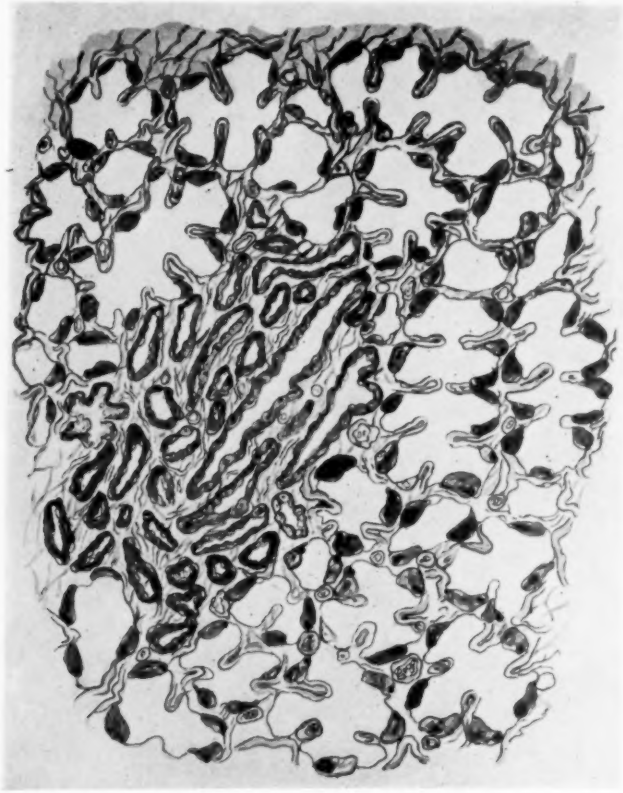

FIG. 3. Alternating resting and functioning units.

(*b*) *Adaptation of the other structures of the units.* In animals with low gas exchange requirements (amphibia) the air-spaces of the lungs are completely lined with epithelium and the lungs are perfused only periodically, the circulation in the organ as a whole being short-circuited from the right ventricle to the aorta, just as it is in the human fetus. In animals with higher gas exchange requirements (birds) the lungs consist of one large air-sac with a separate air inlet for fresh air and an outlet for used air; one capillary network being placed in the center of the air-sac, there is no tissue layer between the capillary surface and the air in the sac, the breathing surface being altogether naked.

Man stands between these two extremes as far as gas exchange requirements are concerned. Accordingly, the internal surface of the human lung is naked only in part, and while the organ as a whole cannot be shunted from the circulation, partial shunting is possible within the individual units. This we construe to be a structural adaptation for increased unit function. For years anatomists have debated the question as to whether the air-spaces of the human lung are lined or naked. The answer from our hypothesis would be that it is lined at some times and naked at others, depending upon the alternating periods of rest and active function. Resting units are fully lined, their walls are thickened and they have the retracted appearance of what Seemann [29] has designated as "physiological atelectasis." The recent and particularly exact studies of Verzar [30] have given us conclusive proof of the truly physiologic nature and prevalence of such atelectatic areas in the lungs normally. The functioning units are expanded, their walls thinned out, their epithelial lining discontinuous, with the cells few and far between, leaving naked stretches where the capillary surface is exposed, with only an extremely thin mesenchyme membrane separating it from the air-spaces, as was so well demonstrated recently again by Clara.[31]

In the resting units the circulation is for nutrition the blood supply of which Daly [32] has recently again shown to be coming from the bronchial arteries by anastomoses with the capillary net of the air-spaces derived from the pulmonary artery. That these capillaries are thus perfused alternately by the nutritional circulation from the bronchial artery and a functional circulation from the pulmonary artery has been claimed already by Havlicek.[33] Perfusion for nutrition demands the intervention of a mesenchyme matrix different in quantity and in quality from that required for functional circulation. The original mesenchymal conditions prevail in the resting units which are being perfused only for nutrition, while in the functioning units the mesenchymal layer is softened and thinned out into a membrane of extreme delicacy adapted to functional circulation and filtration, and this constitutes the breathing surface in the functioning lung units.

The tidal volumes of blood are distributed between the functioning units by means of the functional capillary bed. Some blood is always held in the resting units as a blood depot which varies in proportion to the number of resting units. The existence in the lungs of such a blood depot was first assumed by Rappaport [34] and has been fairly substantiated by the recent work of Hochrein,[35] Pfeiffer, [36] Sjoestrand.[37] Some blood passes the lungs by way of these depot channels which thus serve as shunting channels of the pulmonary circulation. Being shunted from the breathing surface of the lung units, the perfusion in these channels is greater as the requirements for gas exchange are less, as for example in sleep, and, on the other hand, is markedly diminished when the gas exchange requirements are increased, as in exercise, and a large proportion of the lung units are in active function. This accounts for the high oxygen tension difference between the alveolar

air and arterial blood at rest, and its disappearance during exercise, as found by Bock et al.[38]

We conceive of increased capillarization to be the key to increased unit function in the lungs, just as it is in some other organs such as the kidney. Increased capillarization and increased capillary filtration result in the consistency changes in the endothelial membrane and the mesenchyme matrix above described, resulting in greater efficiency in the functional mechanism, and are a part of increased intrinsic lung function.

(*c*) *Self-Cleansing.* Intrinsic unit function requires the most intimate exposure of as extensive and delicate a breathing surface as the momentary gas exchange requirements demand. This intimate exposure is present only for short periods and in a fraction of the units. But, when it occurs, the air-spaces are flooded by an abundant fluid stream which drains out into the lymphatics and air-passages, not only the fluid but also dissolved material and desquamated cells in the lumina of the air-spaces, laden with digested foreign matter. The self-cleansing rôle of the fluid stream was already appreciated by Irwin.[39] Intrinsic unit function automatically affords a self-cleansing of the air-spaces and of the breathing surface, so that we consider self-cleansing as a component of intrinsic unit function. The efficiency of self-cleansing depends upon the efficiency of the intrinsic function as a whole and fails when that function is disturbed.

*E. Lung Function (Intrinsic Unit Function) and Ventilation (Extrinsic Breathing).* These are two altogether separate functions which are intimately correlated. The neuromuscular apparatus of breathing acts in both, but the distinction between intrinsic function and extrinsic breathing is very definite inasmuch as the former depends upon the permanent tonus, while the latter is accomplished by the periodic contractions and relaxations of the neuromuscular apparatus. This concept rests on the outstanding work of Hess[40] which established the fact that the neuromuscular apparatus of breathing (in the diaphragm, chest wall and bronchi) functions by maintenance of neuromuscular tonus, that the permanent state of inflation of the lungs is maintained by the permanent tonic component, and that the superimposed pulmonary excursions are accomplished by the shifts in neuromuscular tonus manifesting themselves in the periodic increased contractions and partial relaxations of the neuromuscular apparatus. Demonstration of the exact rôle of the "self-controlling," i.e., "proprioceptive" reflexes in the regulation of both the permanent tone as well as the periodic contraction of the neuromuscular apparatus of breathing was the contribution of Fleisch.[41]

Like capillary perfusion, intrinsic unit function is uninterrupted but operates in alternating groups of units. It depends on the constant negative pressure, that is, the permanent thoracic traction, which is maintained by the basic tonus of the neuromuscular apparatus of breathing.

Like cardio-circulatory function, ventilation, that is, the movements of

the lungs, is periodic, depending upon the rhythmic contractions and relaxations of the neuromuscular apparatus of breathing.

Intrinsic unit function, however, is regulated in accordance with the momentary requirements of the tissues of the body and, like similar functions in other organs, is controlled by regulation simultaneously through chemical hormonal and vegetative nervous stimuli. The neuromuscular apparatus of breathing which acts both in intrinsic lung function and in ventilation is under the combined control of the vegetative and the voluntary (cerebrospinal) nervous system. For the transmission of stimuli from the vegetative to the voluntary sphere, which is necessary for this combined control, Nature has provided the proprioceptive reflex regulation, so called by Hoffmann [42] who discovered these reflexes and revealed their significance. The permanent tonic activity of the neuromuscular apparatus of breathing which is active in intrinsic lung function is brought under vegetative nervous control by these proprioceptive reflexes. The manner in which the vegetative (regulatory) nervous system controls the tone and automatic contractions of the breathing musculature by way of the proprioceptive fibers traveling in the pulmonary vagus, has recently been discussed by Nakanishi [43] in a particularly illuminating fashion. The periodic ventilatory activity of the apparatus of extrinsic breathing, while chiefly under voluntary control, is also subservient to intrinsic lung function which is under vegetative nervous control.

Ventilation is thus always adapted to the momentary level of intrinsic lung function. With the demand for increased lung function, as in exercise, there takes place an increase in the intrinsic unit function and also in the number of functioning units, and with this ventilation must also increase proportionately. We conceive that there is considerable variation between individuals in their capacity for the adaptation of intrinsic function. Some individuals can meet the requirements for gas exchange by fewer units functioning with greater efficiency, while in other individuals the same demand must be met by calling upon the simultaneous function of a greater number of units. In the latter case quantity has to make up for quality, the air turnover must be proportionately greater and, consequently, the ventilation must be relatively increased. Thus it is seen that ventilation may compensate for intrinsic lung function to a considerable extent.

On the other hand, within the limitations of his capacity an individual may compensate for deficient ventilation by increased intrinsic function. We conceive that the true capacity for pulmonary function as a whole is the efficiency of the intrinsic lung function factor. Excessive ventilation is more often a sign of low pulmonary capacity, while low ventilation is more apt to be associated with an intrinsic lung function which is compensatorily increased rather than deficient. Direct support for this contention may be found among others in the work of Herbst,[44] but particularly in the more recent study of Thomas [45] in which he concluded that

It is important to realize that increase in residual air may constitute one factor in a method of increasing oxygenation of the blood and should not be accepted per se as evidence of reduced pulmonary efficiency.

*F. Respiro-Circulatory Correlation.* That there is a definite correlation between the circulatory and respiratory functions is well recognized, although not by any means completely understood. For our purposes we wish to sharply distinguish the correlation which exists in general between ventilation and circulation, and that correlation which we assume to exist between intrinsic lung function and the pulmonary circulation proper. The ventilatory excursions of the chest promote the venous return to the right heart in one phase, and the action of the left heart in the other. This represents the correlation between ventilation and cardiocirculatory function in general. In our conception of intrinsic lung function the degree of functional capillarization in the lung is of fundamental importance, as are certain phenomena in the pulmonary circulation such as the blood depot function and shunting as above explained. Just as extrinsic breathing and intrinsic lung function are correlated with each other, so we conceive that the cardio-circulatory function of the body as a whole is coördinated with ventilation so as to adapt the changes in the pulmonary circulation to the demand of increased lung function.

## Fibrosis and Emphysema as Intrinsic Lung Failure

It is obvious that these concepts of intrinsic lung function must materially affect our ideas concerning the pathogenesis of fibrosis and emphysema. We have already indicated that one of the essential features of intrinsic lung function is the self-cleansing mechanism by which the air-spaces are kept clear and the breathing surface clean, by the constant and rapid elimination from the tissues of the lungs of everything which interferes with the forces operating in air-space expansion and breathing surface creation. This includes the elimination of large quantities of fluid, the disposal of many waste products reaching the lungs from the blood, and the disposition of extraneous matter reaching the lungs by inhalation and also through the desquamation of cellular material. We suggest that interference with the normal fluctuations in the consistency of the capillary endothelial membrane and also of the mesenchyme matrix, tends to bring about an increase in density and a hardening of the consistency of the mesenchyme. This materially affects its characteristic permeability and its mobility and thus interferes with its adaptations required in the operation of intrinsic unit function. This hardening and decrease of mobility also interferes with the self-cleansing function and thus leads to fibrosis with obliteration of the units affected. These changes may result from the inhalation of foreign matter, as in silicosis, or they may be the effect of inflammatory processes of various kinds, or they may be due to irritating toxic substances coming in from the blood, or they may be due to abnormal circulatory changes associated with disease

of the heart or the kidney. Fibrosis and obliteration of the affected units are the result.

For whatever reason various lung units may thus be excluded from intrinsic function they still remain subject to the ceaseless air-space expanding force of thoracic traction. Wherever capillary filtration and the associated alternations in the consistency of the mesenchyme matrix have ceased, the degree to which any individual lung unit may resist or must yield to expansion will depend upon the intensity of the thoracic traction force on the one hand, and upon the extent and rate of the increase and hardening of the mesenchyme on the other.

Increase and hardening of the mesenchyme matrix obliterating the air-spaces constitutes fibrosis.

Expansion of the unit without simultaneous breathing surface creation constitutes emphysema.

These two processes go hand in hand and are, therefore, practically always to be found in combination. Sometimes fibrosis will prevail over emphysema, while at other times the emphysema prevails over the fibrosis. It thus lies in the very nature of intrinsic lung function coördinated with the mechanical forces in operation, that a unit permanently excluded from function must either become transformed into a fibrotic band or nodule which may either yield or resist to breathing, or it must be expanded into an ever greater air-space the elements of which are being gradually stretched out of existence. When both of these processes occur in a conspicuously large number of units we speak of pulmonary fibrosis and emphysema, which thus represent a manifestation of chronic failure of intrinsic lung function.

Clinically the term emphysema is applied to permanent distention of the lungs to a degree which normally prevails transitorily in the increased function which occurs during exercise.[4, 5] Associated with this is a permanent increase in the residual air content of the lungs, which in turn implies a proportionate restriction of their vital capacity. As in exercise so in emphysema expansion of the lungs beyond the rest volume takes place in response to a demand for increased intrinsic lung function, which is responded to by the simultaneous function of a greater number of units rather than a greater efficiency of the intrinsic function of the individual units. Just as in exercise so in emphysema there is an individual limit to the possible expansion of the organ and to the feasible number of simultaneously functioning units compatible with the requisite degree of ventilation. Ventilation must always increase proportionately with the increase of simultaneously functioning units. The permanent state of expansion and the periodic excursions of the lungs both represent the activity of the neuromuscular apparatus of breathing. The state of expansion depends upon the state of the basic tonus, and the periodic excursions upon the rhythmic contractions of this apparatus.[40, 41] This is a reciprocal arrangement so that one can increase

only at the cost of the other: if the basic tonus must increase to hold the lungs in greater permanent expansion, then the periodic contractions must diminish in amplitude, that is, ventilation must suffer in efficiency. Hence, if the number of functioning units must be increased beyond a certain limit this can take place only at the cost of ventilation.

Increase in the number of simultaneously functioning units represents a type of compensatory increase in intrinsic lung function, which results in better utilization of the lung air, i.e., relatively increased oxygen absorption. This has its limitations beyond which improvement in intrinsic function must be bought at the cost of decreased ventilation, i.e., carbon dioxide retention. This type of compensatory increase in intrinsic lung function takes place also when the interference is primarily with ventilation for some reason, as in obstruction to movements of the chest such as chest deformities, conditions immobilizing the diaphragm, or those interfering with bronchial function as in asthma and bronchial obstruction, etc.

With progressive obliteration of an increasing number of lung units more of the available units are called upon for replacement, so that the number of simultaneously functioning units increases as a matter of compensatorily increased lung function. This necessarily implies a corresponding increase in the permanent expansion of the lungs, and when this goes beyond the limit compatible with the requisite degree of ventilation we have emphysema associated with restriction of vital capacity.

This emphysema, however, is still compensatory in nature, although it may persist throughout life. But, in the final analysis it is only functional not structural in nature, and should the patient die during this phase little evidence of this emphysema will be manifest in the structures of the organ. This explains the great discrepancy between the clinical and the pathologic findings of emphysema.

When fibrous obliteration of the units reaches such proportions that the requisite number of units for compensatory function are no longer available, the force of thoracic traction acts to keep the still available units in constant expansion and tends to gradually overexpand them, so that the air-spaces become dilated and thinned out and may reach the stage of bullae so characteristic of advanced emphysema. These bullae represent air-spaces formed by the coalescence of lung units in which intrinsic function, particularly breathing surface creation action, has ceased. Emphysema thus represents air-space production without corresponding breathing surface creation.

We may conclude, then, that just as pulmonary fibrosis may in the final analysis be interpreted as failure of self-cleansing, so emphysema in the final analysis may be explained as failure of breathing surface creation.

Fibrosis and emphysema thus represent a form of organic asthenia of the structures which function in breathing surface creation and in self-cleansing. This asthenia manifests itself by the insufficiency of the erectile

force of the capillary blood flow and the drying-up of the stream of tissue fluid which normally pours into the air-spaces. Accompanying this there are functional changes in the quantity and quality of the mesenchyme matrix which plays the paramount rôle in both breathing surface creation and in self-cleansing. The result is an ever decreasing partitioning of the air-spaces, that is, loss of internal breathing surface, and increasing coalescence of the air-spaces, with no evidence of where the tissue elements have disappeared. The structures in which the reservoir of the function-bearing mesenchyme has become exhausted disappear in the self-cleansing process which acts ceaselessly in coördination with the uninterrupted air-space expanding force. Whole units and groups of units are thus cleansed out and ever larger bullae are thus produced.

This organic asthenia may represent a congenital weakness of the organ, or the result of damages and injuries produced by a great variety of pathological processes occurring during the life of the individual, and, finally, it may be the result of the natural involution process of old age.

All of these factors are naturally subject to many variations in the same individual and particularly between different individuals. Thus, the great differences in individual predisposition to fibrosis and emphysema in the younger age group are explained, as well as the variations in the period at which they develop among the more aged.

## Pulmonary Failure and Decompensation

We have thus indicated that according to our conceptions pulmonary fibrosis and emphysema represent a chronic decompensation of the function of the lungs. Clinically this is regularly manifested by the decompensation syndrome the most outstanding symptom of which is dyspnea.

As fibrosis and emphysema become more advanced we observe clinically episodes of more acute pulmonary decompensation. These take the form of more acute dyspnea, cyanosis, with evidence of pulmonary edema. These attacks may vary in intensity and duration and will often clear up temporarily. Finally, however, all cases arrive at the stage of acute pulmonary edema which has usually been interpreted to mean cardiac failure. According to our observations, however, it is not the heart which fails but rather it is its continuing compensatory effort which intensifies the pulmonary embarrassment. For, the more lung units are out of function the more the circulation must increase in the remaining available units. But, with such a vast proportion of the lungs' units failing to perform their function, the blood continuing to come into the lungs only increases the burden upon the decreasing number of still functioning units, and so these too become unable to arterialize and transmit the blood. We then observe complete failure of the lungs, manifesting itself in pulmonary edema. The self-cleansing function and the breathing surface creation having already been taxed to their full limit, also fail entirely, and the patient dies of acute pulmonary decompensation or failure.

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# THE DIFFERENT CLINICAL GROUPS OF XANTHOMATOUS DISEASES; A CLINICAL PHYSIOLOGICAL STUDY OF 22 CASES *

By S. J. THANNHAUSER, M.D., Ph.D., and HEINZ MAGENDANTZ, M.D.,
*Boston, Massachusetts*

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From the Medical Clinic of the Boston Dispensary and Tufts College Medical School, Boston.

## Introduction

The group of lipid diseases comprising xanthomatosis, Gaucher's disease and Niemann-Pick's disease has been considered in the newer literature, following the idea of L. Pick,[85, 86, 87] as a disturbance of the lipid metabolism of the whole organism. In essential xanthomatosis, cholesterol and cholesterol esters, in Gaucher's disease cerebrosides, and in Niemann-Pick's disease sphingomyelins are involved.

This paper deals with essential xanthomatosis only, on the basis of observation of different clinical groups of this disease. We have set as our task the elucidation of the pathogenesis of this disease and to investigate whether the basic disturbance is in the intermediary cholesterol metabolism or whether it lies in the xanthoma cell (foam cell) itself, the characteristic feature of the xanthomata.

To approach this problem it is necessary to discuss in detail our present knowledge of the normal metabolism of cholesterol, and to consider whether the facts warrant the general assumption that xanthomatosis is due to a disturbance of the cholesterol metabolism in the whole organism.

## The Metabolism and Function of Cholesterol

Whether the body is able to synthesize and to disintegrate the sterol-skeleton is a fundamental question. The possibility of a synthesis of the sterols has been investigated from different points of view. Gamble and Blackfan,[42] carrying out balance experiments with infants on a milk diet, believed that cholesterol was formed in the body as shown by a greater output than intake. My coworkers and I [128] showed similar results in balance experiments on adults (if the present knowledge based on the work of Schönheimer,[116] that plant-sterols are not absorbed, is applied to the figures of our experiments). At the same time Schaber and I [129] were able to substantiate the fact that the total amount of sterols increases in eggs during incubation. Today the synthesis of sterols in the organism is demonstrated beyond doubt in many experiments. I may mention the experiments of Schönheimer [110] on laying hens, and also the studies of Jenke and myself [133] on dogs with bile-fistulas, which establish the fact that 2 gm. of bile acids are produced daily from dogs independent of the sterol content of the food.

It is not definitely known in which organs and cells the sterol-synthesis is accomplished. Cholesterol-determinations in cases of yellow atrophy of the liver [131] and experiments on hepatectomized dogs,[132] however, point to the liver. In both of these conditions we found a decided drop of total cholesterol in the serum.

The mechanism of the formation of the sterol-skeleton in the body,

however, is entirely unknown. It is not even possible to determine whether cholesterol and bile-acids are formed from proteins, carbohydrates or fats in the animal organism. Studies relating to this question by my coworkers Jenke [130, 134, 56] and Schindel [105, 106] on dogs with bile-fistulas produced no clear results. Only experiments on lower plants hint at the material from which the sterols in plants may be synthesized. According to Massengale, Bills and Prickert,[73] the amount of ergosterol formed by Saccharomyces cerevisiae depends on the amount of sugar present, and sugar is the only organic foodstuff in the basal medium supplied in these experiments. Polysaccharides occasioned the formation of greater amounts of ergosterol than did the monosaccharides. It is noteworthy that the presence of sulphite decreases the sterol production of yeast in such a solution (McLean and Hoffert [69]).

The destruction of the ring system of cholesterol in the metabolism has not yet been proved. Patients suffering from nodular xanthomatosis with a very large amount of cholesterol in the blood exhibit a considerable loss of cholesterol when kept for a long period on a cholesterol-free diet. In two balance experiments about 20 gm. of cholesterol disappeared within seven weeks without being recovered in the stools. The output of sterols in the period mentioned was low (Schönheimer,[115] Schilling [104]). Analyzing the whole bodies and excreta of rabbits, cats and mice after feeding cholesterol-rich diets, Menschnik and Page,[74] Schönheimer and Breusch [112] recovered only a part of the amount of cholesterol given. These experiments, however, indicate merely that cholesterol, fed and retained, cannot be found again with digitonin precipitation. A recent paper by Bertha Ottenstein [82] clears up this supposed disappearance of cholesterol in the body, by showing a disintegration of the sterol-skeleton due to the action of bacteria in the intestine. She demonstrates further that colon bacilli from the large intestines are particularly active in this respect. Thus a deficit of cholesterol in balance-experiments may be due to bacterial destruction and not to disintegration of the sterol-ring system in intermediary metabolism. A gap in the sterol-skeleton produced only by irradiation of ergosterol with the formation of vitamin D is no proof of metabolic disintegration. As long as derivatives of sterols, indicating a decomposition of the sterol-skeleton, are not discovered, the destruction of the sterols in the intermediary metabolism is not conclusive. Summing up, it may be said that the synthesis of the sterol-skeleton in animals is evident but the destruction of the sterol-molecule in the metabolism is not proved.

The changes which the body is enabled to make in cholesterol are significant but few. By means of an esterase the alcoholic hydroxyl is esterified with different fatty acids. The esterification of cholesterol produces a change in its physical properties important for its absorption and transportation in the organ fluids as well as for the composition of the cell-lipoids. Although an esterase is present throughout the body, the liver plays an

important rôle in determining the ratio of cholesterol to cholesterol esters. Schaber and I [131] showed that the esters are diminished in the serum in cases of parenchymatous liver disease, a fact confirmed by many investigators.

Schönheimer [111] substantiated the presence of dihydrocholesterol in the serum and in tissues in normal humans, later on demonstrating an increase of dihydrocholesterol in a patient with nodular xanthomatosis.[115] These experiments (Schönheimer and Hrdina [116]) gave evidence that dihydrocholesterol in the tissue indicates a reduction-process in the body. Genuine reduction-processes are not known in the intermediary metabolism. There are combined processes of hydrogenation and dehydrogenation coupled with an oxygen-acceptor. It may be that the dihydrocholesterol in the tissue originates from such a process. In contrast to dihydrocholesterol the isomeric coprosterol does not occur in the tissue or in the intermediary metabolism. Allocholesterol, which is supposed to be the unsaturated stereo-isomeric sterol of coprosterol, is not discovered in the body according to Schönheimer.[114] Thus coprosterol must originate from cholesterol in the intestines. In the formation of coprosterol from cholesterol a change in the steric configuration must be accomplished on carbon-atom 5. This steric transformation is supposed to be produced by activity of bacteria. In a recent paper Schönheimer,[117] by means of an ingenious method of adding deuterium instead of hydrogen to the double bond, indicated the probability of a mechanism of the steric transformation of cholesterol to coprosterol. First, the stero-isomeric cholestenone is formed from cholesterol by oxidation and then undergoes reduction to coprostenone and coprosterol. The possibility of a steric transformation of cholesterol in the body is of importance because the bile acids are members of the coprosterol-series. Although coprosterol and allocholesterol have not yet been recovered in the intermediary metabolism it was thought to be possible that the bile acids originate from sterols of the coprosterol-series. Indeed in our [130, 134] experiments on dogs with bile-fistulas the injection of allocholesterol and coprosterol increased the output of bile acids. However, in dogs the amount of bile-acids produced daily was found to be so great, namely, about 2 gm., that the bile-acid formation must originate from a biological synthesis of the sterol-skeleton in the liver and not from a metabolic transformation of sterols already existing in the body. The results of our experiments were confirmed by Schönheimer [118] and his coworkers by adding deuterium on the double bond of cholesterol and feeding this deuterium containing cholesterol to animals. The bile acids produced afterwards in the organism did not contain deuterium. Thus we may assume that cholesterol absorbed or synthesized in the metabolic processes is excreted as unchanged cholesterol in the bile and in the intestines. There cholesterol is transformed for the most part into coprosterol and probably undergoes a bacterial destruction to an unknown extent. The ability of bacteria to destroy organic ring compounds is one of the most important facts in the equilibrium of the organic

world. Thus the uni-cellular organism prevents the preponderance of cyclic organic compounds, which are synthesized by higher plants and animals, over aliphatic substances in nature. The presence of certain bacteria in the bowels therefore is wisely provided for in all animals.

The ability of the intestine to excrete cholesterol is not the same in all animals. The herbivorous animals cannot excrete cholesterol in noticeable amounts although they are able to absorb animal cholesterol experimentally added to their plant food. Therefore, atheromatosis might be produced experimentally by feeding cholesterol to herbivorous animals. The question arises, which kind of sterols is absorbed in animal and human bodies? The experiments of Schönheimer [116] and his coworkers demonstrate that neither herbivorous nor carnivorous animals absorb plant sterols. Only small amounts of ergosterol are absorbed. It is a noticeable fact that dihydrocholesterol, although it is formed in the intermediary metabolism and excreted in the intestines, is not reabsorbed. Cholesterol is the only animal sterol which undergoes absorption from the intestines. It is excreted in the bowels and reabsorbed to a large extent.

This marvelous selective absorption of sterols, unexplained in its mechanism, is of great importance for the sterol metabolism, protecting the body against an accumulation of sterols. The fact that cholesterol is synthesized in the metabolism prevents a deficiency of cholesterol in the organism due to an unsatisfactory absorption. In regard to the excretion, however, diseases may originate from an accumulation of cholesterol due to an unsatisfactory discharge.* This matter of clinical interest will be discussed later on.

The function of cholesterol itself in the metabolism is rather doubtful, although its wide occurrence in the animal kingdom is supposed to give a hint of its necessity. The main function of cholesterol is indicated in the fact that cholesterol and cholesterol esters are present in a constant percentage in every lipoid mixture occurring on the surface or within the cell. Cholesterol is a hydrophobic colloid while the monoaminophosphatides like lecithin are hydrophylic colloids. The diaminophosphatides occupy a middle position between the two so far as their behavior towards water is concerned. The correct mixture of the lipoids in the cells depends on the presence of an adequate amount of cholesterol. Thus one of the important functions of cholesterol is seen to result from its physical properties, especially in regard to the equilibrium of the lipoid mixture, which controls the exchange of fluid as well as the exchange of fat-soluble material in the cell.

Some authors attach significance to the fact that cholesterol neutralizes hemolytic substances, for example saponins, different glycosides, and animal venoms. To accomplish this the double bond and the hydroxyl group in the sterol molecule must be available. Esters and saturated sterols exhibit

* Bareda [11] proved that a clinical tolerance test by feeding cholesterol in oil and examining the serum cholesterol after a certain time gives unsatisfactory and not uniform results because the test depends on too many uncontrollable factors.

no anti-hemolytic efficiency. In a similar way cholesterol is supposed to be effective against some of the bacterial toxins. This conception is based on its action in vitro against tetanus toxin. Furthermore, it is observed that in most febrile infectious diseases blood cholesterol is reduced at the climax and also in the terminal stages of infectious diseases. It may be admitted, that while cholesterol forms insoluble addition products with anti-hemolytic substances, like tetanus toxin, in vitro, most of these substances, or reactions occur neither in normal nor in the diseased body. The claim then, that the main function of cholesterol must be a detoxifying one is not satisfactorily proved.

Hypotheses referring to the function of cholesterol are as numerous as they are fragile, so that the mention of a new hypothesis may be presumptive. The presence, however, of dihydrocholesterol in the tissues, as discovered by Schönheimer [111] can be explained by the assumption that there is an oxidation-reduction system in the body within which cholesterol-dihydrocholesterol plays the same rôle as succinic and fumaric acid do in an already known system of this kind.

The cells in the body break down and are rebuilt. In this process cholesterol becomes available and is needed. In addition to its metabolic utilization cholesterol is synthesized, excreted and accompanies neutral fat wherever fat is transported in the body. The concentration of cholesterol in the blood, therefore, depends on these different occurrences, so that an increase or decrease of cholesterol and cholesterol esters in the blood is not due to a one uniform cause.

Hypercholesteremia, whether due to cholesterol esters or to free cholesterol, is a symptom which indicates that the excretion of cholesterol does not keep pace with the endogenous and exogenous supply. Simultaneously with the symptom of hypercholesteremia, cells appear in different organs filled with lipids which are mainly sterols. These cells, which are called foam-cells, according to their appearance, or xanthoma cells according to their content, may after some time give up their cholesterol to the blood. There remains a granulomatous scar tissue consisting of giant cells, lymphocytes, and connective tissue. Before we enter into the discussion of the mechanism of the xanthoma formation, different clinical pictures of the xanthomatous diseases will be presented.

## Xanthomata of Tendons and Tendon Sheaths

*Case 1.* R. S., a 65-year-old Jewish widow, noticed first the appearance of "burning lumps" on the knuckles of the third finger of each hand at the age of 35. When 55 years of age, similar lumps developed above both heels, and at the age of 62 a small node appeared on the right elbow.

She stated that a tumor of the uterus and both ovaries had been removed when she was 42 years old. She had gained much weight after the operation. She had been married three times, and had no children.

One brother had small but similar lesions on his fingers.

She was an elderly obese woman of the matron-type, not icteric. She had no

FIG. 1. Case 1. Xanthomatous nodules of the tendon and tendon sheaths of the hand.

FIG. 2. Case 1. Xanthomatous nodules on both Achilles tendons.

xanthelasma. Liver and spleen were not palpable. In the extensor tendons of both third fingers were circumscribed xanthomata measuring about 3 by 6 cm. movable only with movement of the tendon in the region of the phalangometacarpal joint. There was another small node on the fifth finger of the left hand and large xanthomata in the region of both Achilles tendons.

Changes in the right knee joint, clinically and roentgenologically were characteristic of osteoarthritis, but no cystic bone lesions were present. The patient was admitted to the hospital on 10/21/35.

The following table gives the cholesterol findings in the blood serum.

| | Serum Total Cholesterol | Free Cholesterol | Cholesterol Esters |
|---|---|---|---|
| 10/22/35 | 360 mg. % | 200 mg. % | 160 mg. % |
| 10/29/35 | 368 | 240 | 128 |
| 11/7/35 | 347 | 191 | 156 |
| 11/19/35 | 351 | 187 | 164 |
| 11/26/35 | 345 | 148 | 197 |
| 12/2/35 | 338 | 158 | 180 |
| 12/17/35 | 420 | 200 | 220 |
| 1/15/36 | 388 | 198 | 190 |
| 4/17/36 | 394 | | |
| 6/2/36 | 440 | 124 | 316 |
| 7/9/36 | 423 | 163 | 260 |
| 9/10/36 | 390 | 70 | 320 |
| 11/13/36 | 364 | 113 | 251 |
| 2/20/37 | 284 | 100 | 184 |

A cholesterol-free diet was begun on 10/22/35 and continued until discharge on 11/29/35. Thyroid extract was administered as follows: from 11/20/35, gr. 1, b.i.d.; from 11/20 to 11/2935 gr. II, t.i.d. The thyroid was discontinued on 11/29/35.

A small subcutaneous nodule appeared below the right knee cap during the diet treatment. A biopsy from the node in the tendon of the third right finger showed the xanthoma to be intimately connected with and situated between the fibers of the tendon. The section was composed of dense interlacing cellular strands and bands of collagenous tissue interspersed by innumerable varying sized groups of large foam cells. Among these swollen xanthoma cells were occasional binucleated cells and rare mitotic figures. There were no large giant cells.

A smear from the first specimen showed many cholesterol crystals. Analysis of dry tissue: total cholesterol 9 mg. per cent; total phospholipids 11 mg. per cent.

There was no recognizable change in the size of the lesions of the tendons during the period of cholesterol-free diet, which, however, the patient did not follow strictly. Small xanthelasma-like yellow lesions in the skin of the nose at the site of the pressure of her eye-glasses appeared in December 1936.

*Case 2.* R. S., a 55 year old salesman, brother of Case 1, had noticed nodes on his knuckles for several years. He had never been seriously ill and had no complaints.

He showed a small xanthoma on the extensor tendon of his right fourth finger at the first interphalangeal joint. He also showed circumscribed swellings of both Achilles tendons, 4 by ½ cm. The liver and spleen were not palpable.

| | | |
|---|---|---|
| Serum total cholesterol | 210 | mg. per cent |
| " free cholesterol | 107 | " " " |
| " cholesterol esters | 103 | " " " |

*Discussion.* In 1879, Calcott Fox [39] in England and Carry [27] in France first described patients suffering from xanthomata of the tendon sheaths.

The patient described was a member of a family which had suffered from so-called "gout" for three generations. The diagnosis of "gout" was previously made in the girl described, although at the age of seven she had yellowish xanthomata plana in addition to the tendon sheath nodules. The

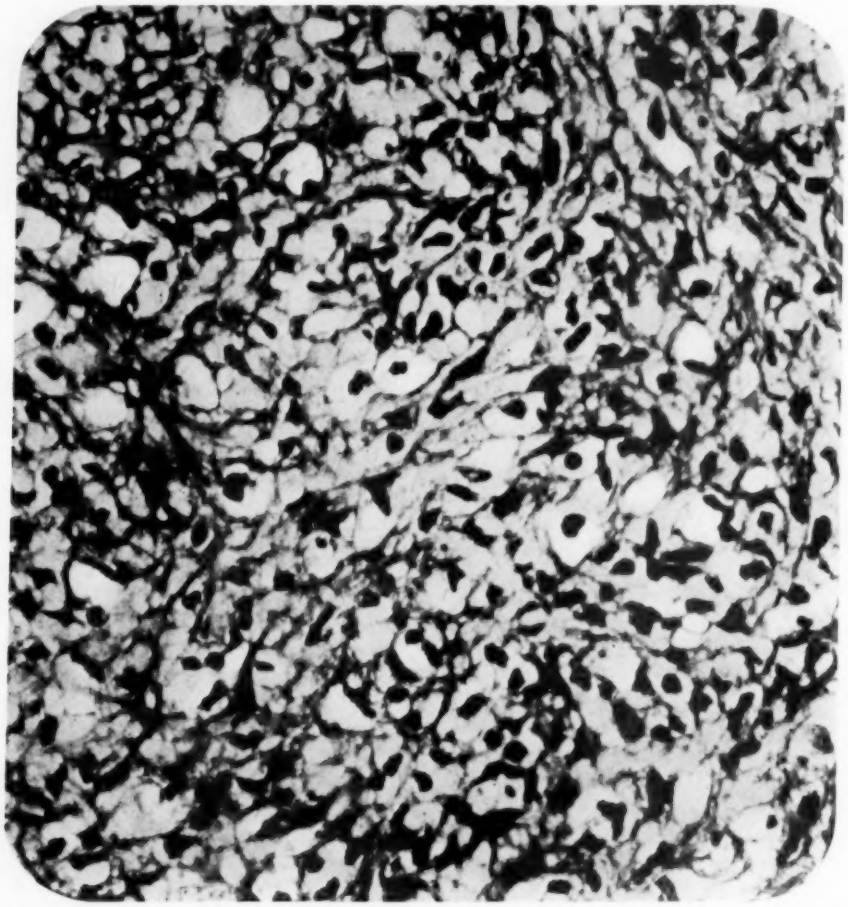


FIG. 3. Case 1. Histological picture of xanthoma cells in an excised tendon xanthoma of the hand.

tendon sheath xanthomata are named the "gout form of xanthomata" even in later publications and textbooks. "Gout form" is a misleading term in these cases. True gout is due to a retention of uric acid and a deposit of its sodium salt in the gaps of connective tissue leading to nodules as the result of inflammatory reactions. Xanthomatous nodules are not produced by a deposit of cholesterol outside the cells, but by a disease of certain cells which contain cholesterol intracellularly. These cells undergo destruction due to their abnormal contents, and a granulomatous scar remains. Besnier called such a new growth "Xanthoma en tumeur." In 1882

Startin[127] reported six cases. In 1889 G. Lenzen and K. Knauss[62] presented the first good pictures of such a patient in Virchow's Archiv. Brachet-Monnard,[20] Poensgen,[89, 90] Balzer,[10] Richter,[99] Lowe,[65] Arning and Lippman,[6, 7] Ganat,[43] Ochs, Schmidt,[107, 108] Schönheimer,[115] Buerger,[25]

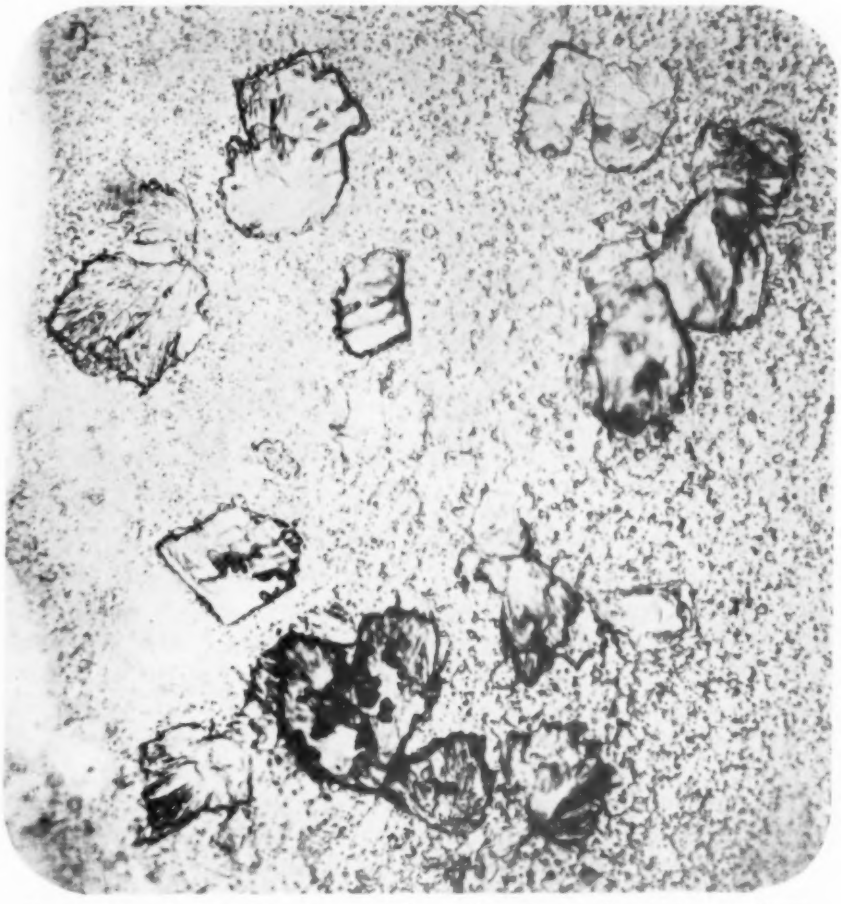


FIG. 4. Case 1. Cholesterol crystals in a softened part of a tendon xanthoma.

Raeder,[96] Wile,[156, 157] and many others described such cases. In the surgical literature Beekman,[15] Brochard,[21] Buxton,[26] Janick,[55] Dean Lewis,[64] Romiti,[99a] Ragins,[96a] F. Young and C. T. Harris,[159] emphasized the fact that xanthomata of the tendons are part of the tendon. Thus they cannot mechanically be separated from the tendon.

One of the tendon sheath xanthomata of our Case 1 was excised by Dr. Levenson for chemical analysis. The nodule could only be partially removed because the tumor was a part of the tendon of the third finger of the right hand.

*Comment.* Sister and brother (Case 1 and Case 2) are elderly persons.

In the sister the first tendon sheath nodules developed at the age of 35, the tumors on the Achilles tendons at the age of 55. The brother first noticed nodules on his hands at the age of about 40. The name "xanthoma juvenile" sometimes used in the literature for the xanthomatous tendon sheath is therefore not justified, although in many cases the development starts in

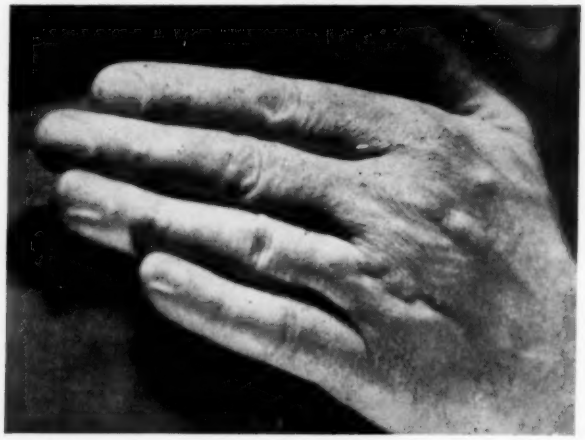


FIG. 5. Case 2. Xanthomatous nodules of the tendon and tendon sheaths of the hand.

the first years of life and even a congenital case has been reported. It is noteworthy that both our patients showed no other xanthomata of the skin although the tendon sheath xanthomata had been present for almost 30 years. The pinhead sized xanthelasma at the pressure point of the spectacles on the nose developed only recently.*

*Histological Findings.* The main piece of tissue consisted of young fibroblasts and granulomatous tissue. This granulomatous tissue in which giant cells were found, invaded the normal tendon. Large cells with one or two nuclei were scattered throughout the nodule. These cells with a foam-like opaque protoplasm (foam cells) contained fat, cholesterol and cholesterol esters and monoaminophosphatide. The foam cells are found massed in the reticular tissue. They are supposed to develop from reticulum cells and histiocytes. The characteristic picture of a xanthoma, where it may be encountered, consists of scattered or aggregated large foam

* While this paper was in press, two papers appeared, one by L. van Bogaert, H. J. Scherer, and E. Epstein [19a] with the title "Une forme cerebrale de la cholestérinose généralisée" and the other by E. Epstein and K. Lorenz [35a] describing a similar case. These cases of van Bogaert, Scherer and Epstein showed severe neurological disturbances, ataxia, atrophies of different groups of muscles, disturbance in speech. Later on bulbar symptoms and flaccid paralysis of all extremities developed. The neurological symptoms began at the age of 12, progressed until the age of death, of 40 years. At the age of 33 only tendon xanthomata developed. Excellent histological pictures show foam cells and deposits of cholesterol crystals in the central nervous system. None of our cases with tendon xanthomata (1, 2, 7, 9, 10, 11, 12, and 13) showed any psychic or neurological abnormalities. The cases of van Bogaert showed normal and high normal serum cholesterol like our cases 2 and 10. The combination of central nervous system xanthomatosis and tendon xanthomata has not been described until now.

cells occurring in granulomatous tissue with fibroblasts and exudate cells or in old connective scar tissue.

One area of the excised nodule, the size of a pinhead, was softened. Microscopically the yellow detritus showed typical cholesterol crystals and a few needles, probably cholesterol esters.

*Chemical Findings.* The cholesterol content in the serum of Case 1 was never extremely high. However, figures above 400 were observed. Our early observations on this patient showed an inverse ratio of cholesterol-cholesterol esters. During the period of the cholesterol-poor diet, a normal ratio was restored but the total cholesterol remained at the same level, despite a cholesterol-poor diet taken over a long period of time. The brother, who had smaller nodules, exhibited high normal total cholesterol but an inverse ratio of cholesterol-cholesterol esters. In the cases of tendon xanthomata described in the literature, the total cholesterol values are very high and the cholesterol esters especially are increased. The inverse ratio of cholesterol-cholesterol esters suggests an involvement of the liver although clinical signs of hepatic disease are absent. Neither patient was ever jaundiced. It is significant that despite the patients' ages no unusual signs of vascular disease were found.

In this and in most of the later described cases of xanthomatous diseases, phospholipids are determined quantitatively. Monoaminophosphatides (lecithin-cephalin) and diaminophosphatides (sphingomyelin) are determined separately by our new method (Thannhauser and Setz [135]). Up to the present time the phosphorus value obtained using Bloor's method was multiplied by 25 and the figure thus obtained designated as lecithin. However, the so-called lecithin value comprises the monoaminophosphatide (lecithin-cephalin) and diaminophosphatides (sphingomyelin). Not only are these substances notably different in their chemical constitution, but also in their physiological significance. With our method of precipitating the sphingomyelin complex as Reinecke compounds, and separating and weighing the sphingomyelins, it is possible to determine sphingomyelins gravimetrically and to evaluate the rest of the formed total lipid phosphorus as lecithin and cephalin. Using serum from patients suffering from xanthomatous diseases, this method demonstrates whether an increase of cholesterol in the serum and tissue is accompanied by an increase of monoaminophosphatides (lecithin-cephalin) or by an increase of diaminophosphatides (sphingomyelin) or by a simultaneous rise of all three lipids.

In the serum of Case 1 the total phospholipids were increased. It is shown that the increase of phospholipids results mainly from a rise in the monoaminophosphatides (lecithin-cephalin). The sphingomyelins show only a small rise. In the analyzed tissue of the tendon sheath xanthoma, there was considerable increase of cholesterols and monoaminophosphatides but only traces of diaminophosphatides could be detected. These findings demonstrate that in the examined case an increase of sterols in the serum

as well as in the tissue is combined with an increase of monoaminophosphatides (lecithin-cephalin) but not with an appreciable increase of sphingomyelins. The physiological significance of this finding is unknown, but clinically it is important that the xanthomatous diseases show, in addition to the outstanding symptoms of increased cholesterol in serum and tissue, increased monoaminophosphatides, while in Niemann-Pick's disease the outstanding finding is increased diaminophosphatides (sphingomyelin) (E. Klenk [13]).

## Xanthoma Tuberosa

*Case 3.* Female of 40 years had known she had diabetes for two years. Had taken no special diet. Sugar excretion was always around 1 per cent (10 to 20 gm.) daily. She noticed peculiar "warts" of yellowish color on both elbows five years previously. Blood examination showed slight lipemia. On both elbows there were typical xanthomata tuberosa. She became sugar-free on diet, but the tuberous xanthomata did not disappear. Total cholesterol 570 mg. per cent.

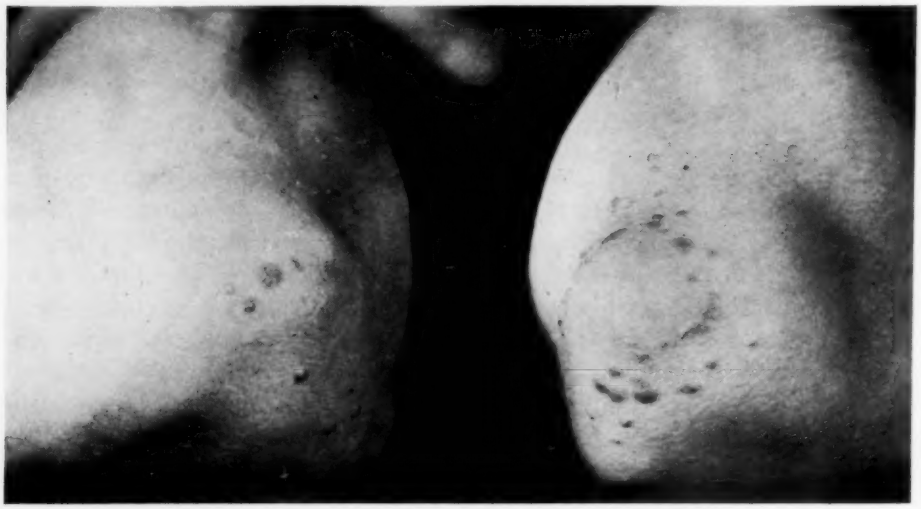


Fig. 6. Case 4. Xanthomata tuberosa on both elbows.

*Case 4.* The patient is a 30 year old physician suffering from chorioretinitis of the disseminated type, affecting both eyes. He had had difficulty with his vision for three years. Despite search, a definite etiology could not be found. At almost the same time he noticed small lesions about the elbows, knees and buttocks which were diagnosed as xanthomata tuberosa. His main complaint was fatigue for the previous three years. He had no fever, no loss of weight. His appetite was good and he carried on his profession satisfactorily. Two children were living and well. Physical examination revealed no vascular disease. Blood pressure 110 systolic and 90 diastolic. Urine findings negative.

On both elbows there were xanthomata tuberosa. The pea-sized xanthomata had a yellow color and marked hyperkeratosis on the top of the lesions. Similar lesions were found on the knees and on the buttocks. No other xanthomata were observed. Mucous membranes were free.

The creases on the palms of both hands were yellow, of a carotine-like color. His blood serum showed the same color due to carotinemia. Quantitative determination of carotine was not carried out at this time.

Blood sugar (fasting) 86 mg. %.
Sugar tolerance curve, 7/7/36: Fasting 86 mg. %; ½ hour 154 mg. %; 1 hour 102 mg. %; 2 hours 78 mg. %; 3 hours 53 mg. %; 4 hours 93 mg. %.

This rather flat tolerance curve does not suggest a latent diabetes.

| | | |
|---|---|---|
| *Serum:* | Van den Bergh | 0.542 (Direct, negative) |
| | Total fats | 1088 mg. % |
| | " cholesterol | 476 |
| | Free " | 125 (Normal ratio, free: esters) |
| | Cholesterol esters | 351 |
| | Sphingomyelins | 243 (Normal 100 to 150 mg. %) |
| | Total phospholipids | 437 (Normal 200 to 350 mg. %) |
| | Monoaminophosphatide, total lipids—diaminophosphatide: 194 mg. % (Normal 100 to 150 mg. %) | |
| Analysis of stromata of red blood cells | | |
| | Diaminophosphatide | 3.7 mg. %, low normal (Normal 4 to 5 mg. %) |
| | Total lipids | 10.6 " " " " ( " 10 to 15 " ") |

*Comment.* We have thus far considered only simple forms of what we consider to be xanthomata tuberosa. The above described nodules of the tendon sheaths as well as xanthomata multiplex disseminata, which will be illustrated later, are erroneously designated as xanthomata tuberosa. Tuberous xanthomata are nodular elevations of the skin. The nodules are usually observed isolated, not confluent or aggregated in small groups. The shape is irregular and they may vary from pea size to the size of a chestnut. Their favorite location is the extensor surface of the arms, especially the elbows, or on the buttocks. The surface usually shows hyperkeratosis and is of yellow or carrot-like color. Xanthomata tuberosa and xanthomata disseminata which are entirely different in size, shape, color and localization are generally confused in the literature. The mucous membrane and larynx are rarely involved in tuberous xanthomata in contrast to the xanthomata multiplex disseminata in which lesions almost always arise simultaneously in the mouth and larynx.

The reason for this confusion may be due to the fact that the histological findings are identical in both xanthomata tuberosa and xanthomata disseminata despite the fact that appearance and localization are clinically entirely different. In both lesions we find foam cells, i.e., cells with one or two nuclei, "Touton giant cells." The amount of fibrous tissue which is found in the nodule surrounding the foam cells varies according to the age of the xanthomatous nodules. In later stages only granulomatous scar tissue may be found. There is no sign of inflammation or vascularization around the nodules on the skin and no papule or pustule formation. This is important in differentiating between xanthomata tuberosa and the eruptive form of papulo-pustular lesions which occur in severe diabetes and symptomatic hypercholesteremia.

Xanthomata tuberosa may be combined, as in Case 3, with mild diabetes. In these cases of rather mild diabetes the lesions of xanthomata tuberosa (which do not itch) may be the expression of a similar xanthomatous eruption in the pancreas. In 1921 Wijnhausen [154] was able to verify such a coincidence by operation. In his patient xanthomata tuberosa were noticed

34 days before sugar was found in the urine. Frequent attacks of ileus, as in bowel obstruction, accompanied by fever were observed. Operation one year after the onset of the symptoms revealed chronic pancreatitis and tuberous xanthomata in the pancreas. The patient recovered from the operation. The diabetes and the tuberous xanthomata of the skin may be considered the result of the same disease, i.e. xanthomatosis, affecting the skin and pancreas simultaneously. This suggestion has also been mentioned by Rowland.[101] As early as 1880 Gendre [45] reported the case of a patient who had been suffering from mild diabetes and tuberous xanthomata for 10 years. "Malgré la presence du diabète sucré datant de dix ans ce cas ne peut pas être rangé parmi les xanthomes diabétiques."

The eruptive form of papulo-pustular xanthomata, the so-called xanthomata diabeticorum, is entirely different in etiology from the xanthomata tuberosa. Xanthomata diabeticorum are the sequel of a severe diabetes mellitus in the course of which lipemia and hypercholesteremia occur, occasionally producing the itchy papulo-pustular eruptions which appear and disappear.

I should like to emphasize further the importance of differentiating between xanthomata tuberosa and xanthomata disseminata because the visceral organs involved may be predicted by the kind of skin lesions present. Xanthomata tuberosa and plana may be combined, as we shall see later, with endocardial and vascular xanthomata as well as with hepatic and pancreatic disease; while xanthomata disseminata is found with xanthomata of the bones and lungs, xanthomata of the brain and diabetes insipidus.

*Serum Chemistry.* The serum of a patient with xanthomata tuberosa shows high total cholesterol values largely due to increased cholesterol esters. The cholesterol-cholesterol ester ratio is normal or changed in favor of the esters. The monoaminophosphatides (lecithin-cephalin) are markedly increased. The diaminophosphatides (sphingomyelin) are also a little higher than normal but the monoaminophosphatide-diaminophosphatide ratio shows that the increase of total phospholipids is mainly due to the increase of lecithin-cephalin. The glycerides are also considerably increased. The increase of the monoaminophosphatides and glycerides simultaneously with the cholesterol is to be considered a fact evident from many observations.

## "Forme Fruste" of Xanthomatous Diseases

*Case 5.* Mrs. F., 55; main complaint fatigue. For many years easily tired; very active in the household. Physical examination: Mentally quick, haggard lady. The color of her skin is brownish, like a tan (has not exposed herself to sunlight). Both palms of hands and feet and especially the creases of the hands show xanthosis, that is, a yellowish carotin-like color. Sclerae normal color. There are no abnormalities of the inner organs discovered; no signs of hypothyroidism. Urine and blood normal. Basal metabolic rate, minus 10 per cent; blood sugar 85 mg. per cent; bilirubin, van den Bergh 0.5; icteric index 11.

| | Total Cholesterol | Free | Esters | Total P. Lipid | Diaminophos. Sphingomyelin | Monoamino-p. Lecithin-Cephalin | Fat |
|---|---|---|---|---|---|---|---|
| 9/24/35 | 295 mg. % | 103 mg. % | 192 mg. % | | | | |
| After cholesterol-poor diet..... | 276 mg. % | 75 | 201 | 290 mg. % | 81 mg. % | 209 mg. % | 389 |

*Case 6.* E. de S., 48 years. Family History: Diabetes in several members of his ancestry. Patient has six healthy children. Patient reports that 10 years ago he had a trace of sugar in the urine. Sugar disappeared without keeping to diet. Six years ago he was examined in Paris and hypercholesteremia was found without other symptoms. Total cholesterol at this time was 455 mg. per cent. Four months later, after a diet poor in fats, the total cholesterol was 320 mg. per cent. Patient kept on this diet for six years. Cholesterol determination repeated several times during the past year showed values of total cholesterol around 200 mg. per cent. Basal metabolic rate normal on several occasions.

The main complaint of the patient is fatigue. He is sometimes depressed and feels uneasy. He lives in the tropics now; has to be very active in his business. His mental agility is quick, in contrast to his physical fatigability.

*Physical findings:* Man of normal figure; no signs of hypothyroidism. The skin exhibits xanthosis on the trunk as well as on the extremities (see case 4); especially the palms of the hands and feet and the creases on the palms show a yellowish carotine-like color. The lungs are normal. Heart is normal in size; systolic murmur at aorta. Blood pressure 135 systolic and 85 diastolic. Liver and spleen not remarkably enlarged. Blood and urine normal. Blood sugar 102 mg. per cent; bilirubin (Van den Bergh) 0.5 mg.; icteric index 20.

*Blood chemistry:*

| Total cholesterol | Free | Esters | Total P. Lipid | Diaminophos. Sphingomyelin | Monoamino-p. Lecithin-Cephalin |
|---|---|---|---|---|---|
| 216 mg. % | 50 mg. % | 166 mg. % | 309 mg. % | 112 mg. % | 197 mg. % |

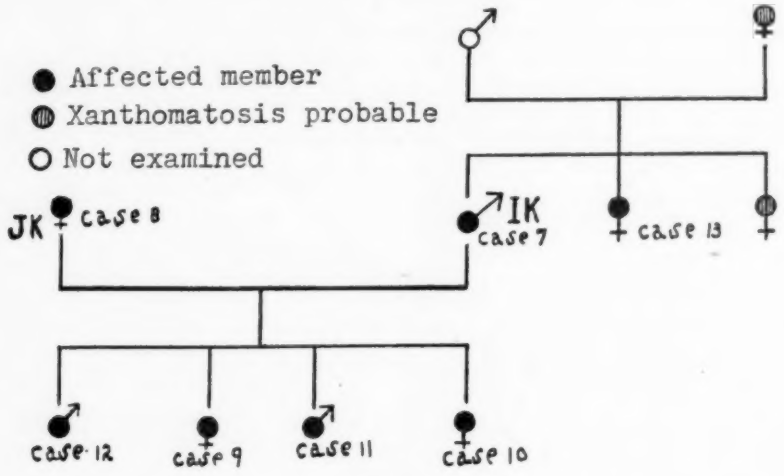
We report these cases as "forme fruste" of xanthomatous diseases because they have the same features as patients exhibiting xanthomata tuberosa (hypercholesteremia, xanthosis (carotinemia), inclination to mild diabetes) but no skin xanthomata. These patients are often diagnosed as hypothyroids because they exhibit physical fatigability, high blood cholesterol and sometimes basal metabolic rates on the lower borders of normal. In contrast to patients suffering from hypothyroidism, these patients are mentally very alert, they are not anemic, they perspire easily and have a smooth skin. They are not slow in their activities, but they fatigue easily. The cases reported by Edelmann [34a] with xanthosis, fatigability, diffuse pains in muscles, complaints of irritability of the gastrointestinal tract, belong to this group. We determined the carotine content of the serum quantitatively in a case which we have seen recently and found 0.4 mg. per cent (normal 0.05 to 0.1 mg. per cent). We believe that the forme fruste of xanthomatous diseases, characterized by hypercholesteremia, xanthosis and caroti-

nemia, associated with fatigability and inclination to mild diabetes, is seen not infrequently if distinguished from hypothyroidism.

### Xanthomata Tuberosa and Plana and Tendon Xanthomata

We were fortunate to discover an entire family suffering from xanthomata of the skin as well as of the tendon sheaths. G. K., a female child (Case 9), aged 11, was observed at the Children's Hospital. We are indebted to Dr. Blackfan and Dr. Diamond for the privilege of seeing this child and for the opportunity to study the entire family, whose case histories follow.

Family Tree of Family K




*Case 7.* Mr. I. K., 50 years old, male, Jewish plumber, noticed painless swellings on knuckles of both hands when he was about 30 years old. During the last 5 to 10 years he also noticed swellings develop on both heels. Two to three years ago, he first suffered from attacks of substernal pain which were diagnosed as angina pectoris and responded to treatment with nitroglycerin.

He was the father of four children, all of whom showed evidence of xanthomatosis (see family tree); his mother had brown swellings on the eyelids; one sister (Mrs. Ch, Case 13) had xanthomata of tendons; another sister is supposed to have xanthelasma.

He was moderately obese, not jaundiced. His eyelids showed no xanthelasma. Lungs and heart were found to be normal on physical examination. Electrocardiogram normal. Liver and spleen not definitely enlarged.

On the third, fourth and fifth fingers of both hands, xanthomata, movable with the tendons on the extensor side, were visible, most pronounced on the first interphalangeal joint. Small nodes were present in the olecranon region. Extensive swellings in the region of the lower third of both lower legs, bulging posteriorly and laterally in the region of the Achilles tendons. These swellings were firm, nontender, larger than those in any other member of his family, measuring 8 by 3 cm.

| | |
|---|---|
| Serum total cholesterol | 265 mg. % |
| Free cholesterol | 105 |
| Cholesterol esters | 160 |
| Total phospholipids | 450 mg. % |
| Diaminophosphatide | 150 mg. % |
| Monoaminophosphatide | 300 mg. % |
| Fat as fatty acids | 496 |

*Case 8.* J. K., a 47-year-old Jewish housewife, first seen October 27, 1936, noticed brownish swellings on both upper eyelids at the age of 23, after her first child was born. When she was 40 years old these lesions had grown considerably and similar lesions had appeared on both lower lids also. No history of serious illness in the past.

*Family history:* See family tree.

She was a markedly obese woman without icterus. There were characteristic xanthelasmata in both upper and lower eyelids, the smaller measuring 3 mm. in diameter, the largest 5 by 20 mm., of soft consistency, elevated 1 to 2 mm. above the level of the skin. No tumors of any tendons were palpable. Liver and spleen were not palpable and not enlarged on percussion.

| | 10/30/36 | 11/2/36 |
|---|---|---|
| Serum total cholesterol | 482 mg. % | 533 mg. % |
| Serum free cholesterol | 129 | 129 |
| Serum cholesterol esters | 353 | 404 |
| Total phospholipids | | 394 |
| Diaminophosphatide | | 132 |
| Monoaminophosphatide | | 262 |
| Fat as fatty acids | | 585 |

On a reduction diet, she lost 31 pounds in seven months. There was no change in her xanthelasma.

*Case 9.* G. K., 11 years old, Jewish schoolgirl (daughter of J. K.) noticed painless nodes appear in the region of both heels at the age of seven. One or two years later similar lesions were seen on the knuckles of several fingers and there was also involvement of the skin of the knees and elbows.

She was an underdeveloped, undernourished, intelligent girl. The xanthomata of the skin were round, brownish-orange colored, flat lesions, 3 to 4 cm. in diameter, with somewhat pronounced margins and sharp borders. The center of these lesions was darker and slightly depressed. Similar, although much smaller tuberous skin lesions were visible in the gluteal folds and flexor aspect of the knees. Besides there were xanthomata of the extensor tendons of the third and fourth fingers of both hands, and larger xanthoma nodes in both Achilles tendons. Liver and spleen not felt. No jaundice. (Figures 7, 8, 9, 10, 11.)

| | | |
|---|---|---|
| 10/26/36 | Serum total cholesterol | 667 mg. % |
| | " free " | 203 |
| | " cholesterol esters | 464 |
| | Total phospholipids | 448 |
| | Diaminophosphatides | 194 |
| | Monoaminophosphatides | 254 |
| | Fat as fatty acids | 423 |
| 3/27/37 | After moderate restriction of animal fat containing food: | |
| | Total cholesterol | 785 mg. % |
| | Free " | 222 |
| | Cholesterol esters | 563 |

The round intradermal lesion on the left elbow was surgically removed and proved to be in intimate contact with the tendon of the triceps muscle. Tissue analysis of the dried lesions, freed as much as possible from subcutaneous fat, showed no sphingomyelin. The total phospholipid content of the dried substance was 12.7 mg. per cent. Total cholesterol of the dried substance was 13.1 mg. per cent.

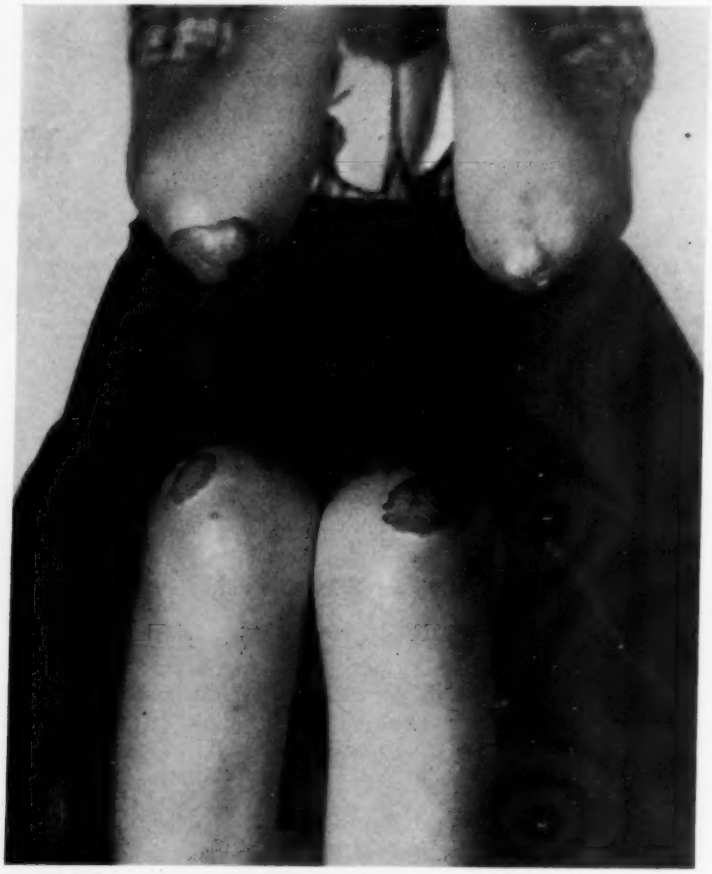


FIG. 7. Case 9. Xanthomata tuberosa and plana on both elbows and both knees.

*Case 10.* S. K., 22-year-old Jewish girl, daughter of J. K., was seen December 7, 1936. She had no complaints but had seen and felt nodes on her heels for two years. She had been obese as a child.

Patient showed slight bulging of the region of the Achilles tendons on both sides, 5 cm. distant from the floor, as the only demonstrable abnormality.

| | | |
|---|---|---|
| Total cholesterol (serum) | 244 | mg. % |
| Free cholesterol " | 83 | |
| Cholesterol esters " | 161 | |

*Case 11.* A. K., 16-year-old Jewish schoolboy (son of J. K.) had no complaints. He showed xanthomata of various extensor tendons of the fingers of both hands and also of both Achilles tendons.

| | |
|---|---|
| Serum total cholesterol | 282 mg. % |
| " free " | 97 |
| " cholesterol esters | 185 |
| Total phospholipids | 303 |
| Diaminophosphatide | 137 |
| Monoaminophosphatide | 166 |
| Fat as fatty acids | 354 |

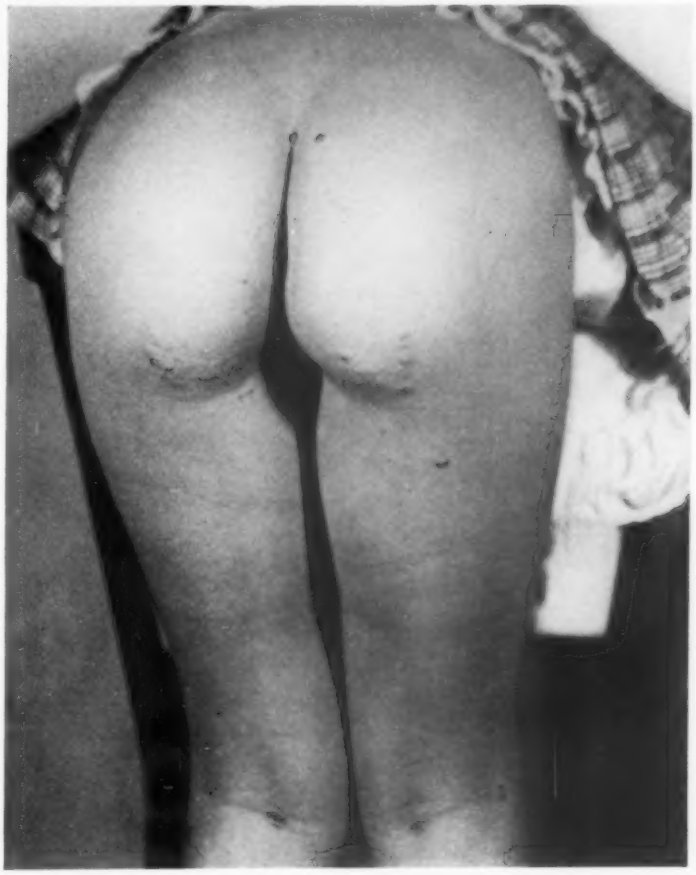


FIG. 8. Case 9. Xanthomata tuberosa on the buttocks.

*Case 12.* H. K., eldest son; 23 years old; student; healthy; no complaints or pathological findings in lungs or heart; normal blood pressure; normal liver and spleen. Examination of left Achilles tendon reveals a pea-sized tendon xanthoma, similar to those of his brother and sister. Chemical findings in the serum: Icteric index 13; Van den Bergh less than 0.5 mg. per cent; carotine 0.25 mg. per cent.

| | |
|---|---|
| Total cholesterol | 400 mg. % |
| Free cholesterol | 100 |
| Cholesterol esters | 300 |
| Fat as fatty acids | 471 |

*Case 13.* Mrs. Ch. (sister of Mr. K.), 51 years old, Jewish housewife (aunt of the 4 K. children) was seen April 17, 1937. She had noticed painless lumps on knuckles of various fingers at the age of 37.

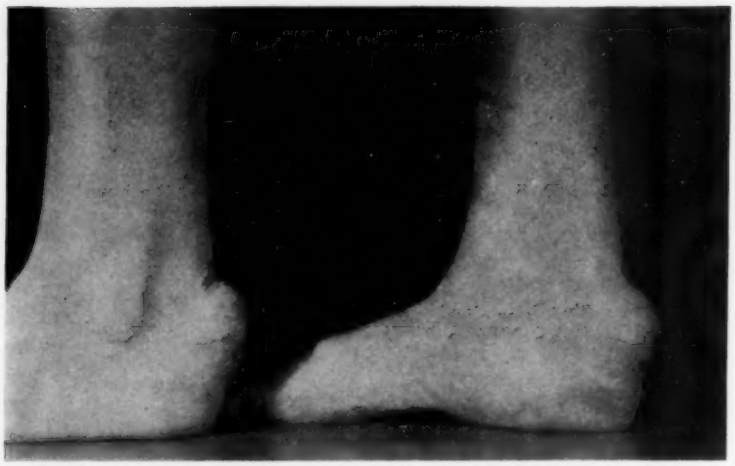


FIG. 9. Case 9. Xanthomatous nodules on both Achilles tendons.

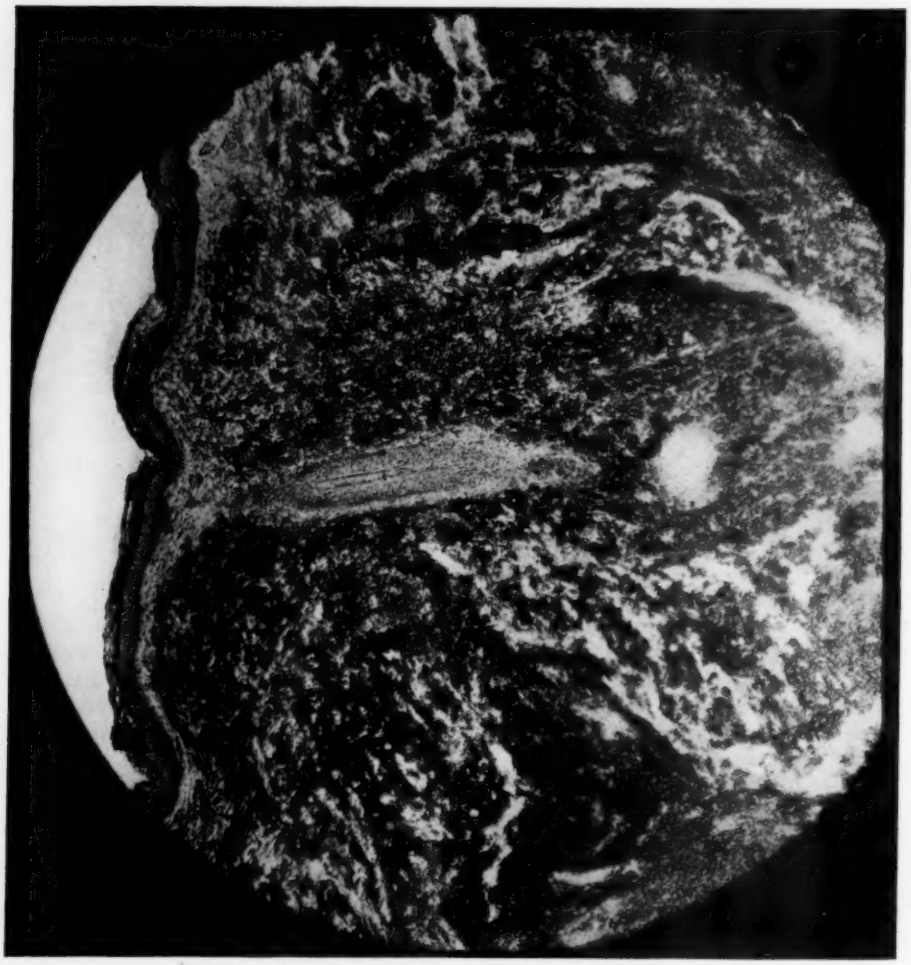


FIG. 10. Case 9. Xanthoma planum; Sudan staining.

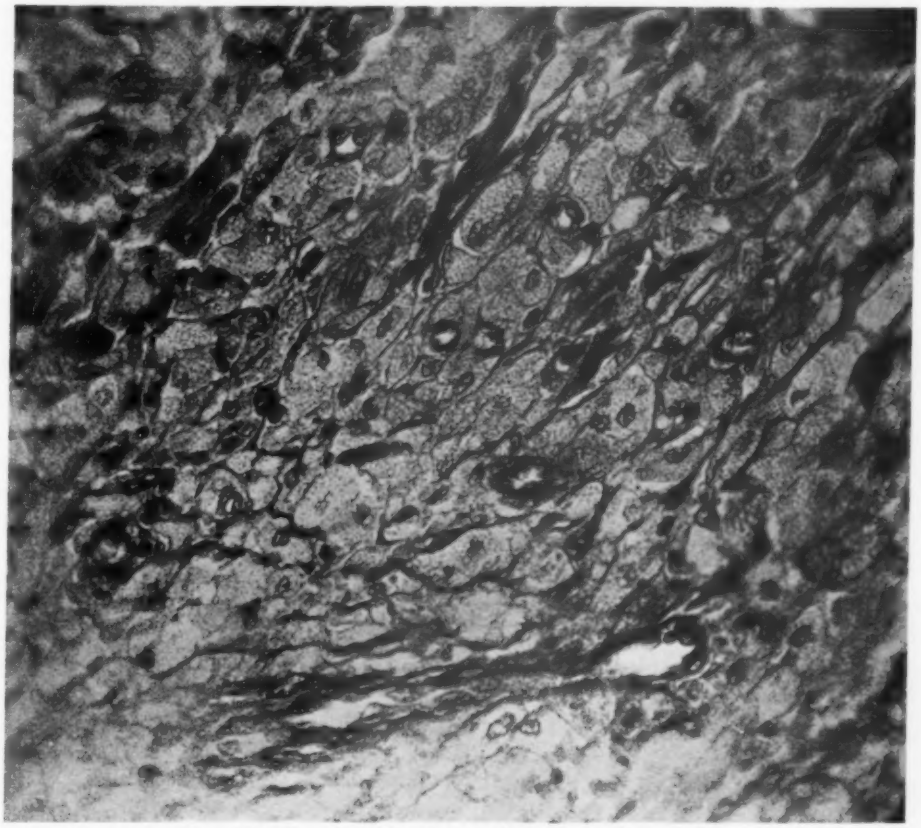


FIG. 11. Case 9. Xanthoma planum xanthoma cells.

She was moderately obese, showed no icterus, no xanthelasma of the eyelids. There were xanthomata of three fingers of each hand, predominantly in the region of the phalango-metacarpal joint, also xanthomata in both Achilles tendons, 2 cm. in diameter and small superficial tuberous nodules in the region of both elbows. Liver and spleen were not enlarged.

| | |
|---|---|
| Serum total cholesterol | 500 mg. % |
| " free " | 183 |
| " cholesterol esters | 317 |
| Total phospholipids | 632 |
| Diaminophosphatides | 83 |
| Monoaminophosphatides | 549 |

*Comment: Heredity:* Case 8 has unusually extensive xanthelasma on both eyelids. Several members of the father's (Case 7) family have tendon sheath xanthomata. All the children of this couple were examined and all were found to have tendon sheath xanthomata. The youngest child, Case 9, has xanthomata plana (xanthelasma), xanthomata tuberosa and tendon sheath xanthomata. It is evident from different cases described in the literature (Török,[138] Raeder,[96] Wile and Dumeling,[157] and from the family tree of this family that heredity is dominant.

Case 9 (11 year old girl) has different kinds of xanthomata of the skin. Later we shall discuss the fact that histological examinations of all kinds of xanthomata reveal a more or less uniform histological structure consisting of foam cells and granulomatous tissue. Because the gross appearance of xanthomata of the skin is different in shape and in color, we have to deal with a nomenclature which describes the different gross appearances of the skin but not different diseases.

Xanthomata plana or xanthelasma are flat xanthomata of carotine-like color or that of chamois leather. In the child, Case 9, xanthomata plana were found on both elbows,* both knees and buttocks. In addition she had xanthomata tuberosa on both elbows, on the buttocks and on the skin of the heels overlying the tendon tumors. Temporarily when she was first observed and once later she even had an eruptive papulo-pustular form of xanthomata on both arms and legs. These eruptive lesions appear and disappear and up to the present time have been observed only on patients suffering from diabetes mellitus.

Later we will show that the papulo-nodular eruption known as xanthomata diabeticorum may occur without diabetes not only in cases such as that just described but also in patients with jaundice and xanthelasma due to xanthomatous liver cirrhosis with a very high serum cholesterol.

We follow Montgomery and Osterberg [76] in separating xanthomata multiplex disseminata from the discussed manifestations of xanthomata of the skin. The disseminated multiple xanthomata does not differ in its histological structure but differs in shape, color and especially in localization, distribution and diagnostic significance. We were unable to find a single case in the literature where disseminated multiple xanthomata of the skin were found in the same patient coincidentally with xanthomata plana and tuberosa, or in patients with tendon sheath xanthomata. But, as we observed in the members of the K. family and other cases cited in the literature, xanthomata plana as well as xanthomata tuberosa are very often combined with xanthomata of tendons.

## Discussion of Coincidence of Xanthomata Plana and Xanthomata of Tendons with Xanthomatous Involvement of Heart, Blood Vessels, and Liver

In 1879, Calcutt Fox,[39] in the first description of tendon sheath xanthomata combined with xanthomata plana, found the mitral valve involved with xanthomata. Poensgen (1887)[89] describes tendon sheath xanthomata, xanthomata plana and tuberosa with aortic involvement in a boy of eight years. Lenzen and Knauss (1889) [62] described and showed a picture of an 11-year-old girl, who, like our patient of the same age (Case 9), had xanthomata plana, xanthomata tuberosa and tendon sheath xanthomata. Their patient died from an intercurrent infection following operation. Autopsy

* We are indebted to Dr. Hilbert F. Day for the excision of one xanthoma plana on the left elbow. 1½ years after this excision there is no recurrence of the xanthoma in the scar.

revealed xanthomata on both pulmonic and mitral valves (patient exhibited intra-vitam unusually loud systolic murmurs) and xanthomatous patches in the pulmonary artery, but the aorta and left carotid showed a xanthoma of the intima simulating a neoplasm which almost occluded the lumen of the vessel. Both coronaries of the 11-year-old child also demonstrated xan-

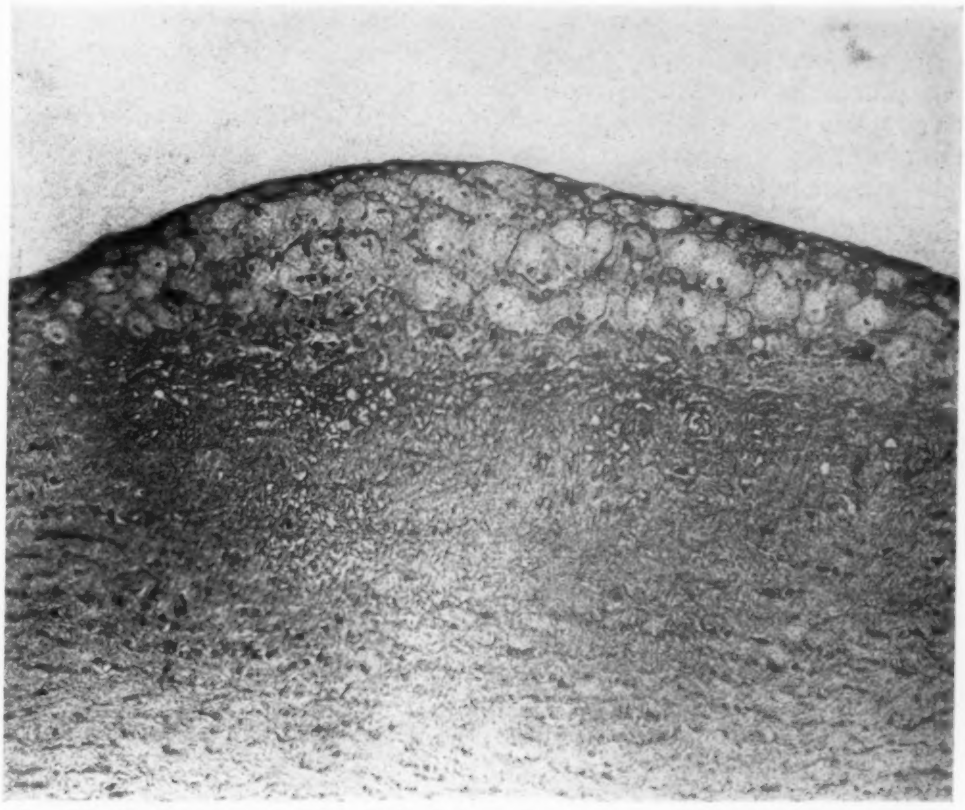


FIG. 12. Xanthomatous nodule of the intima of an artery. (Microphotograph of Dr. Timothy Leary of Boston.)

thomatous patches the size of a pinhead. It is noteworthy that this patient had a sister with the same disease. Similar familial cases with involvement of the heart and the arteries in children are described by Arning (1910),[6,7] and by Lowe (1910)[65] and then by Hess (1934).[51] In all these cases the xanthomatous involvement of the endocardium and vessels was combined with tendon sheath xanthomata and skin lesions of xanthomata plana and xanthomata tuberosa. We should like to emphasize that in the literature, as far as has been able to be determined, not a single case is described where xanthomata multiplex disseminata was found combined with xanthomata of the endocardium and the vessels which we shall picture and discuss later.

At this point we should like to call attention to the fact that hypercholesterolemia is found where xanthomata plana, xanthomata tuberosa, and ten-

don sheath xanthomata are combined with vascular xanthomatous disease, while normal cholesterol values are found in patients suffering from xanthomata multiplex disseminata and xanthomatous bone diseases.

Simultaneous involvement of the liver is rare in cases where xanthomata plana and tuberosa and tendon sheath xanthomata exist over a long period of time without jaundice. Later we shall show that jaundice is the initial symptom of xanthomatous biliary cirrhosis in the course of which (but only after a period of jaundice) the most impressive xanthomatous changes of the skin in the form of xanthomata plana or xanthomata tuberosa may arise. The spleen, the lymph glands and the lungs were not involved in this group of cases but these organs are involved in the group of xanthomata multiplex disseminata of the skin with xanthoma in the brain and the bones.

## Xanthomatous Biliary Cirrhosis

*Case 14.* Female, aged 35 years; wife of a farmer in Germany.[104] One sister suffering from cholecystitis. Married; one healthy child. Patient noticed jaundice in January 1931, for the first time; no pain or other symptoms from the gall-bladder; stools clay-colored, urine dark; itching all over the body. The physician diagnosed gall stones and the patient was operated upon on April 7, 1931. The wall of the gall-bladder was very thick. A gland was found which was intimately connected with the gall-bladder (xanthomatous scar tissue) in the place where the hepatic duct branches. The liver was firm in consistency. There were no stones found and all the larger bile ducts were free of stones. The gall-bladder was removed. After the operation the jaundice increased. Patient grew worse. Treatment with diathermia and carbohydrate and insulin was without effect. Operation again considered by the physician. She was then first admitted to our hospital, November 19, 1931. Weight 52 kg., height 148; severely jaundiced. Several lesions of the skin from scratching. At that time no xanthomata or tuberous xanthomata. Temperature between 37.1° and 37.9° C. Lungs: Normal vesicular breathing; no dullness. Heart: Normal size; no murmurs; blood pressure 140 systolic and 80 diastolic; pulse 76. Abdomen distended; umbilicus deformed. Liver enlarged, five fingers below the costal margin; very firm; surface smooth. Spleen enlarged, firm. There is a small amount of ascites. No *caput medusae*. Urine: trace of albumin, no sugar; urobilin and urobilinogen strongly positive; bilirubin positive; sediment, few leukocytes. Blood: 75 per cent hemoglobin; 3,600,000 red blood cells; 7,200 white blood cells; 1 basophile, 1 eosinophile, 1 stab form, 70 polynuclears, 27 lymphocytes.

Hospital treatment from November 19 to December 20, 1931. Carbohydrate-rich, protein-poor diet with 5 units insulin twice daily. Diathermia of the liver. Weight loss during this time 0.5 kg. From November 26 to December 8, very strong menstrual bleeding. On December 11, sudden rise in temperature to 39° C.; fever continued for five days. Jaundice during the hospitalization was not changed; never evidence of complete obstruction. Never colicky pain. Discharge diagnosis: Biliary liver cirrhosis.

Second admission to our hospital January 11, 1933. Patient reports that no marked changes have occurred since her hospital stay. The menstrual bleeding in the meantime was always excessive. She was inclined to bleeding from the gums and from the genitals apart from menstruation. She felt increasingly weak and without appetite. Stools were not completely acholic. Urine always dark. Physical examination: Weight 43 kg. Jaundice deeper brown. Liver, much larger than at the first admission; almost the whole abdomen is filled by the liver. Its border is

three fingers below the umbilicus. Very firm, surface smooth, no nodules. Spleen the same size as at the first admission; three fingers below the left costal margin. No ascites was found at this time. Surprisingly large lemon-yellow patches were visible on the green-brown jaundiced skin which had not been present the year before. These yellow patches, varying in size from 1 to 10 cm., easy to recognize as xanthomata plana, were found around the eye-lids, on the nose and cheeks, on the abdomen

FIG. 13. Case 14. Xanthoma plana on both eyelids, the nose and the face.

and also on the scar from the operation. On the arms both on the flexor and extensor surfaces and all over the body were extremely itchy papulo-pustular nodules. Around the nodules was a small inflammatory zone of pink color which changed peripherally to bluish-red and finally to brownish. The pustules did not contain fluid or pus but on opening, a soft tissue of yellowish color was seen. Because these

FIG. 14. Case 14. Eruptive form (papulo-pustular form) of xanthoma.

eruptions itched so excruciatingly they had been badly scratched and give the impression of an abraded vesicle with the formation of a crust. The nodules which were not injured by scratching healed without crust formation, but a dark pigmentation remained. Blood: 55 per cent hemoglobin; 2,600,000 red blood cells, 9,000 white blood cells; blood sugar 82 mg. per cent. Bilirubin direct 14.1, indirect 8.1 Van den Bergh's units. Total cholesterol 657 mg. per cent.; free cholesterol 376 mg. per cent; cholesterol esters 281 mg. per cent. Urine: Albumin positive, sugar negative, urobilinogen strongly positive. After a period of strict vegetable diet without any animal cholesterol we noticed an impressive decrease of the total cholesterol, but the inverse ratio of cholesterol-cholesterol esters remained, which is according to Thannhauser and Schaber a sign of liver damage.

| | Total cholesterol | Free cholesterol | Cholesterol esters |
|---|---|---|---|
| February 1 | 657 mg. % | 576 mg. % | 81 mg. % |
| February 14 (cholesterol free diet) | 406 | 314 | 92 |
| February 28 | 152 | 132 | 20 |

On a less strict diet which contained some animal sterol the patient showed after four weeks 296 mg. per cent total cholesterol, 124 mg. per cent free cholesterol, and 72 mg. per cent cholesterol esters. Normal persons who eat a diet free of animal sterol do not change their blood cholesterols (Bareda [11]). Within 28 days the total cholesterol in this patient's case decreased from 657 mg. per cent to 152 mg. per cent. These figures show that 20 gm. of cholesterol disappeared from the blood if we take four liters as the normal amount of circulating fluid. During the vegetable diet period the sterols in the feces were isolated and determined following the technical methods of Schönheimer. The daily amount of sterol in the feces in the beginning of the diet was 1.26 gm.; later it fell to 0.53 gm., and at the end of the diet to 0.827 gm. The attempt was made to isolate cholesterol, dihydrocholesterol and coprosterol quantitatively. Only traces of coprosterol were found but it was impossible to isolate free cholesterol or dihydrocholesterol from the feces during this period. This result is in conformity with the findings of Schönheimer. The sterol structure present in the feces while on the sterol-free diet consists apparently only of plant sterols. It is not evident how the 20 gm. of cholesterol disappeared from the blood. Bacterial destruction of cholesterol in the feces may give an explanation for this important fact according to B. Ottenstein.

The patient grew gradually weaker. She again developed a high fever for the period of a few weeks. Her weight fell to 41 kg. She lost ground rapidly and died eight weeks after she left the hospital. A partial autopsy was performed. Prof. Aschoff, who examined the liver, found a marked cirrhosis and the same xanthomatous changes of the liver tissue which Chvostek described in his case of "xanthelasma and icterus" as xanthoma of the liver.

*Case 15.* (I am very much indebted to Dr. James Waring, Professor of Medicine of the University of Colorado, for the permission to publish this case.)

H. L., housewife, aged 32 years, born in Vienna. Entered Colorado General Hospital November 19, 1935, with the complaint of jaundice and weakness of four years' duration and of yellowish plaques distributed over the body, especially on the face and in the creases of the hands and feet, of about two and a half years' duration.

*Past history:* Patient had measles at seven years, chickenpox at eight years. Never has had scarlet fever, mumps, whooping cough, rheumatic fever, chorea, or venereal disease. Menstrual periods started at 15 years, were regular every 28 days

until spleen was removed two years ago. Has not menstruated since. No menopausal symptoms. One child, nine years of age, a boy, living and well. No other pregnancies. In 1926, the appendix and one ovary were removed.

*Family history:* Mother, living and well, aged 58 years. No tuberculosis contacts. No history of cancer, diabetes, or Bright's disease. No illness in family similar to patient's. No blood dyscrasias; no hay fever; no asthma.

*Present illness:* The patient believes that she was feeling quite well until June 1931. At that time she first noticed that her eyes were yellow. Shortly afterwards her skin became yellow, the urine highly colored and the stools grayish in color. This jaundice gradually increased in intensity and was accompanied by much itching. In September 1931, she consulted a physician in Boston who told her that she had gall stones and advised an operation, which was refused. Patient's weight at the onset of her illness was 160 pounds. In four months, that is at the time she consulted the physician in Boston, her weight had fallen to 132 pounds. In March 1932, she consulted a physician in Cleveland who told her that she had an obstruction of the gall ducts and advised an operation which was again refused. Meanwhile the jaundice had increased in severity and the itching was almost intolerable. In April 1932, she came to Denver and consulted two physicians. A diagnosis of obstructive jaundice was made and an operation advised. At this time, she was told that she had a large liver. The jaundice now showed some variation in intensity and the itching lessened but the patient complained of great weakness. Around both eyelids, xanthelasma palpebrarum was noted. In May 1933, she went to Memphis, Tennessee, where she was operated upon and her spleen removed, but there was no change in the condition following the operation. No gall stones were found, but a narrowing of the common bile duct. About a month before leaving Denver in May 1933, she first noticed yellowish deposits in the creases of her hands. They came on gradually but were rather diffuse in distribution from the very onset, that is, they appeared on the face and on all extremities including both elbows at about the same time. About the middle of 1934, she was quite sick with high fever, increase in jaundice and some delirium. In May 1935, she was given a number of fever treatments at the Colorado Psychopathic Hospital. The fever treatment did not change the condition of the patient.

Patient was seen again by a doctor in Denver in August 1934. She now had yellowish plaques in the creases of the palmar surfaces of both hands. They were each about 2 mm. wide and slightly raised. They were also present on the anterior surfaces of the elbows and on the elbow tips. On the extensor surfaces of the elbows the plaques were enlarged patches and were much raised above the surrounding skin. They were also present over the buttocks. Progress from the fall of 1935 was gradually downward. She had numerous persistent nasal hemorrhages and a little fever off and on much of the time. The first nasal hemorrhage occurred about 1934, lasted about 10 hours and it is estimated that about a pint of blood was lost. Since this time she has had a nose bleed of more or less severity about every six weeks. Epistaxes lasted from six to ten hours and were controlled with difficulty. She does not bruise easily and apparently had not had any petechial spots. She showed marked susceptibility to respiratory infections which were severe and prolonged. With one of these she had an acute suppurative otitis media on the right side. She finally died July 1936, apparently of a typical coronary occlusion.

Physical examination: General appearance: Her entire body is jaundiced, of a dusky bronze color with a tinge of yellow apparent. The coloring is diffuse and fairly uniform with no distinct patches of pigment. No deformity of bony skeleton or skull. No discoloration of mucous membranes. Head: Small nodules apparent on upper eyelids and along the inner canthi. The larger of these have been removed by her physician. Eyes: Some patchy congenital discoloration of the iris. Left

pupil larger than right. Pupils react to light and accommodation. Consensual reflex present. No nystagmus, exophthalmos, visual disturbances or fundal pathology. Conjunctiva and sclera slightly yellow. Visual fields grossly normal. Mouth: Posterior pharynx narrow with large hypertrophied tonsils from which no pus can be expressed. Chest: Organs apparently normal. Diaphragm high posteriorly. Heart: No enlargement noted. Sounds somewhat distant but no murmurs detected.

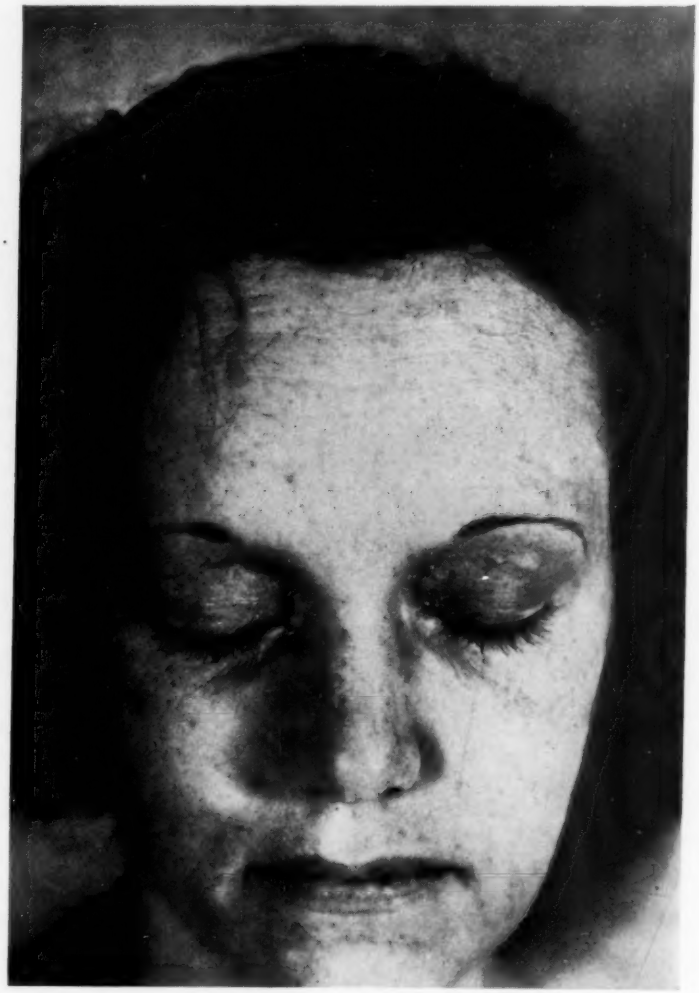


FIG. 15. Case 15. Xanthoma plana and tuberosa on the face, around the eyelids and the papulo-pustular eruptive form associated on the face.

Blood pressure 110 systolic and 70 diastolic. Peripheral vessels soft, pulse regular, rhythmic. Abdomen: Large operative scar. The liver is palpable throughout most of the abdomen. Liver is slightly tender along the left margin. No nodules noted. No fluid detected. No bulging of the flanks. Back and extremities: No deformity, pain, or limitation of motion. On both palms along practically all the flexor creases there are yellowish nodules about 3 mm. above the skin. On the extensor surface of

the elbow there is a large hyperkeratotic mass of the same character. Many similar nodules are distributed along the dorsum of the foot around the toes. Mucous membranes are free from xanthomata. Besides these tuberous and plain xanthomata, a nodular pustular eruption is to be seen, of the same appearance all over the body. There are papules which are excoriated by scratching. (In the photographs this eruptive xanthomata identical with the xanthomatous eruption in cholesterolemia during diabetes mellitus is clearly pictured.) Neurological: Gait and station essentially normal. Romberg negative. Muscular strength decreased. Ability to perform

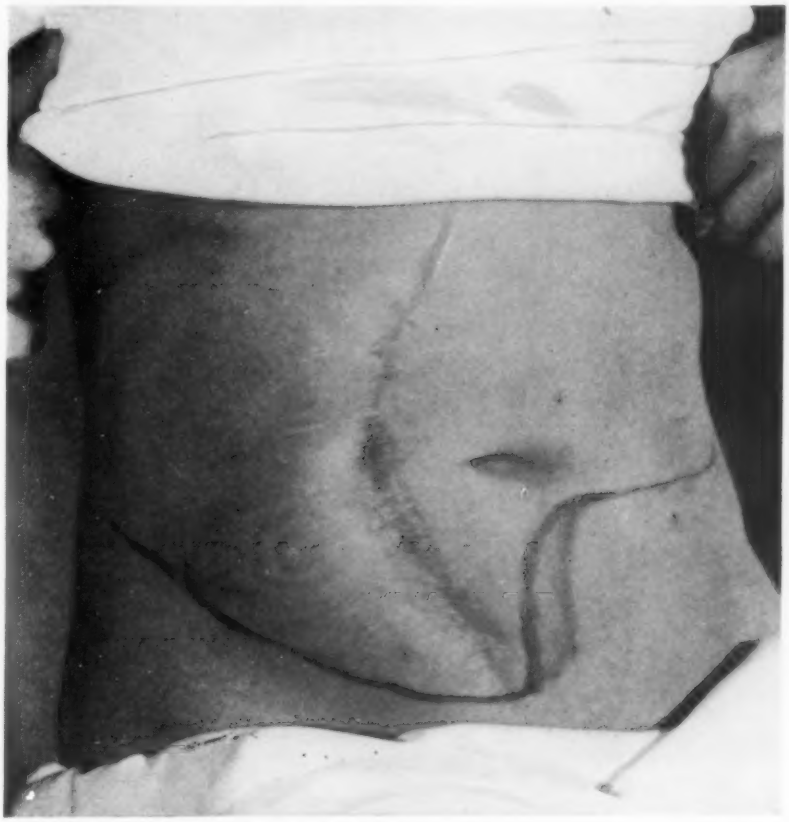


FIG. 16. Case 15. Enlarged liver.

coördinated movements unimpaired. No ataxia, dysmetria, past pointing, athetosis, tremors, spasticity, rigidity, dysarthria, dysphasia, Holmes rebound phenomena or adiadochokinesis. Sensory examination essentially negative. No abnormal subjective sensations other than itching. Knee jerks, ankle jerks, biceps, triceps, radial, patellar reflexes equal and hypoactive; corneal reflex present; superficial abdominal reflexes absent. No Babinski sign or confirmatories. Cranial nerves intact.

May 2, 1935: No roentgen-ray evidence of pathologic changes in bones of skull, chest, pelvis, feet or hands. No definite defects in cranial bones, changes in sella turcica or metaphyses as described in Schüller-Christian's disease.

Urinalysis: color amber, slightly hazy, acid, specific gravity 1.022; trace of albumin; no sugar. Sediment contains a few pus and epithelial cells and many

bacteria; no casts or erythrocytes. Blood examination: Hemoglobin 10.2 grams, erythrocytes 3.2 million per cu. mm.; leukocytes 12,650; polymorphonuclears 80 per cent; lymphocytes 14 per cent; monocytes 4 per cent; eosinophiles 2 per cent. Blood sedimentation: ½ hour 20 per cent, 1 hour 40 per cent. Serological examination: Wassermann test negative. Eagle flocculation test negative.

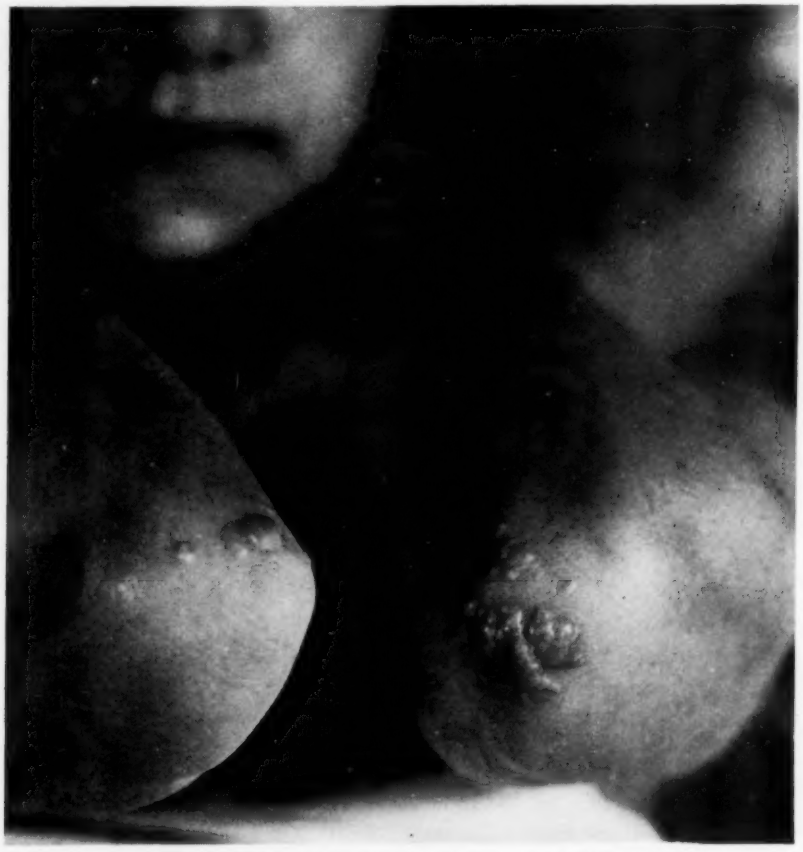


FIG. 17. Case 15. Xanthomata tuberosa on both elbows.

Electrocardiogram showed slight left axis deviation showing definite respiratory shift. Basal metabolism rate, plus 8. Blood chemistry: Sugar (dextrose) 84 mg. per cent; total N.P.N. 33; total cholesterol 400; calcium 10.60. Van den Bergh test 2.66 mg. bilirubin per 100 ml. blood; direct reaction. Icterus index 22. Fragility of red cells normal.

Biopsy: Removal of a xanthoma from the dorsal surface of left elbow (November 19, 1935). (Analysis of the tissue by the Biochemical Institute, University of Denver.)

| Cholesterol | % by weight of fixed tissue |
|---|---|
| Total cholesterol | 1.31% |
| Free " | None |
| Cholesterol esters | 1.31% |
| Phospholipids | 0.117% |
| Equivalent to 0.934% lecithin. | |

*Case 16.* E. H., a 49-year-old Jewish widow, began to have severe itching all over her body at the age of 46. Shortly afterwards eruptions of a pustular character appeared, which bled after scratching. These lesions had been recurring for three years previous to admission. The patient lost 20 pounds in weight within the first year after the onset of the illness. She complained of weakness and had noticed that her urine was at times dark brown. Past and family histories revealed no significant data.

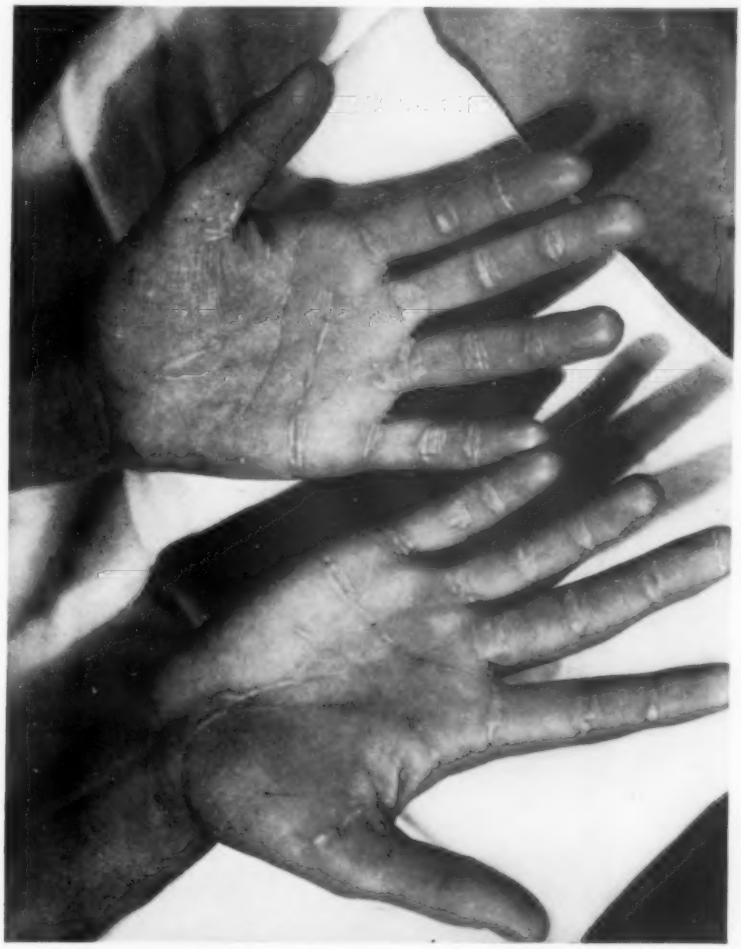


FIG. 18. Case 15. Xanthomata plana on the palms and creases.

When first seen she was icteric and the skin was covered with lesions of discrete varioliform character. They were less than 1 cm. in diameter; on some of them the top was replaced by a crust and surrounded by an inflamed zone. They were fairly symmetrical in distribution but possibly more on back and abdomen than elsewhere. They were superficial and the old lesions represented by faint pigmentation, which persisted for some months (figures 20, 21, 22).

Heart and lungs essentially normal. Blood pressure 160 systolic, 90 diastolic. The liver reached two to three fingers' breadth below the costal margins, the spleen two

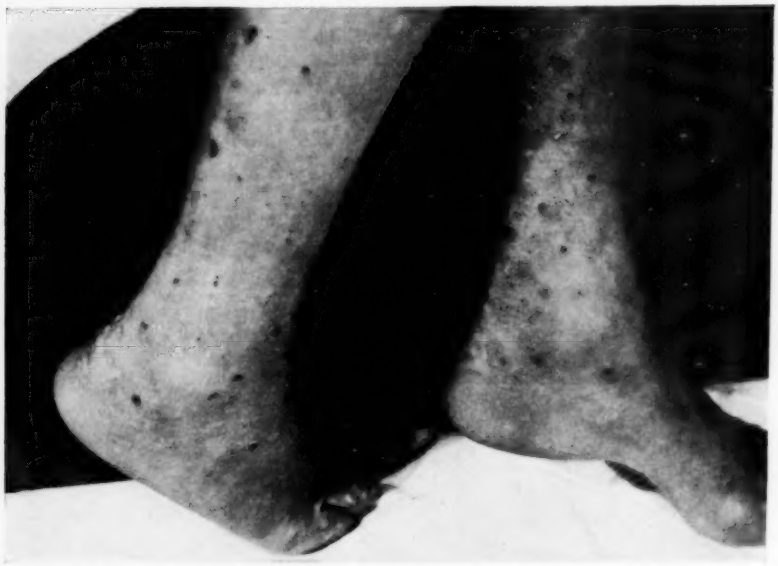


FIG. 19. Case 15. Xanthomata tuberosa and plana and eruptive papulo-pustular form associated on both legs.

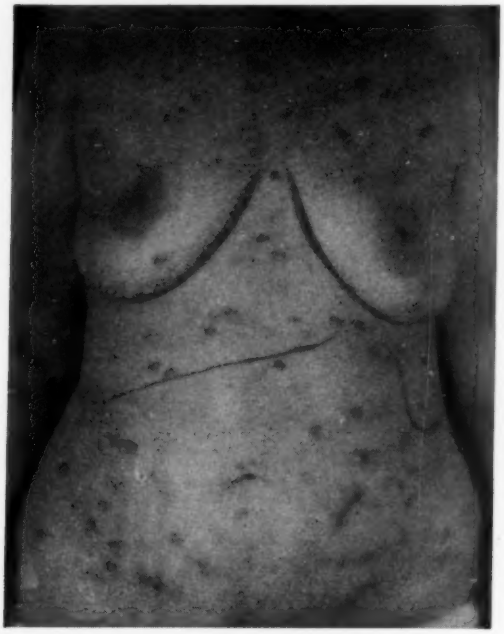


FIG. 20. Case 16. Eruptive form (papulo-pustular form) of xanthoma on the front of the body with enlarged liver and spleen.

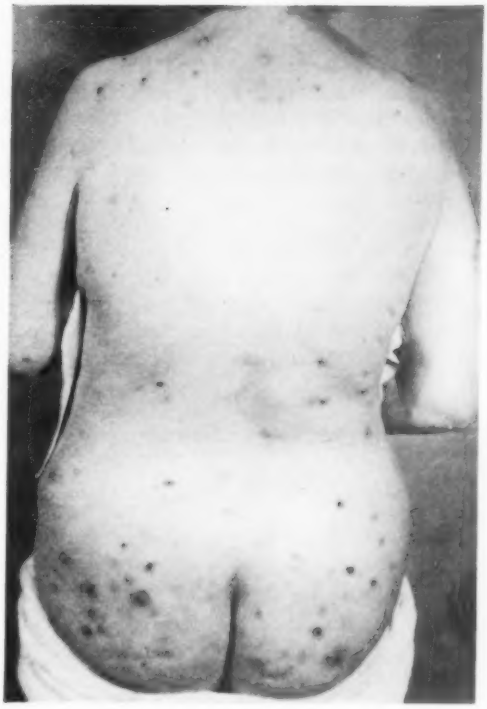


FIG. 21. Case 16. Eruptive form of xanthoma (papulo-pustular form), on the back.

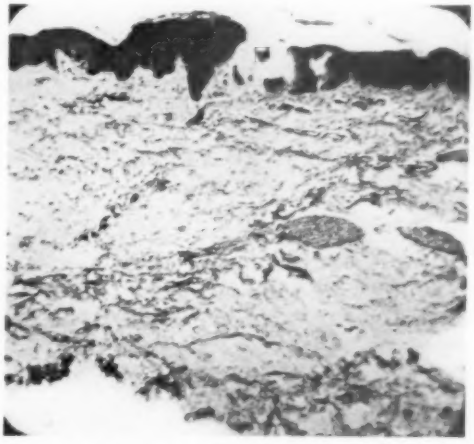


FIG. 22. Case 16. Histological picture of the eruptive (papulo-pustular) form of xanthoma. Notice that no xanthoma cells are seen.

fingers' breadth below the costal margin. Both were firm, smooth, non-tender. No signs of portal obstruction were visible, including the absence of esophageal varices.

The urine contained constantly 0.5 per cent albumin; increased urobilinogen and urobilin; occasional granular casts and rare red blood cells. Icteric index 14 on admission, a year later when the icterus had subsided it was 4.5 and the indirect Van den Bergh reaction less than 0.5 mg. per cent. Non-protein nitrogen 39.6 mg. per cent. Red cell fragility normal. Basal metabolic rate varied between plus 25 and plus 35. Blood sedimentation rate 93 mm. in 1 hour (Westergren). Blood cholesterol 570 mg. per cent.

A year later the patient was put on a cholesterol free diet, following which regime the itching disappeared and the skin lesions diminished, but they did not disappear completely. Patient was given thyroid, gr. 1 daily, in addition to the cholesterol-free diet. Within the last year small xanthelasma lesions developed on both upper eyelids. She had several furuncles which had to be treated surgically. Albuminuria and moderate hypertension remained unchanged as did the enlargement of the liver and spleen.

| | | |
|---|---|---|
| 11/5/35 | Serum total cholesterol | 532 mg. % |
| 11/26/35 | " " " | 606 |
| | " free " | 317 |
| | " cholesterol esters | 289 |

Cholesterol-free diet instituted.

| | 12/3/35 | 12/11/35 | 12/18/35 | 1/8/36 | 1/29/36 | 6/24/36 | 9/4/36 | 11/20/36 |
|---|---|---|---|---|---|---|---|---|
| Serum total cholesterol | 521 | 360 | 329 | 346 | 372 | 300 | 435 | 400 |
| free cholesterol | 290 | 112 | 127 | 137 | 176 | 43 | 138 | |
| esters cholesterol | 231 | 248 | 202 | 209 | 196 | 257 | 297 | |
| Total phospholipids | | | | | | 370 | | |
| Diaminophosphatide | | | | | | 228 | | |
| Monoaminophosphatide | | | | | | 142 | | |

*Discussion and Comment.* The first patient (Case 14) died from hepatic failure due to chronic biliary cirrhosis, having been severely jaundiced for four years. The xanthelasma developed two years after the onset. The eruptive papulo-pustular lesions came and went. During these years a pulsating angiomatous xanthoma developed in a tendon of the left little finger.

Necropsy showed a severe cirrhosis with fat-loaded reticulum cells and foam cells scattered through the liver. There is no question that the hepatic cirrhosis did not result from alcoholism or chronic infection of the bile ducts, but from the formation of xanthomatous tissue which led to connective tissue and scar formation, as in Chvostek's case.

The second patient, Case 15, 32 years of age, died from a coronary thrombosis having been jaundiced for five continuous years. The course of the disease was exactly the same as in case 14. At first there was painless jaundice accompanied by enlargement of the liver and spleen. In both instances operation was performed because of a diagnosis of cholelithiasis but stones were not found. In the second case the surgeon noticed thickened bile ducts but no histological examination of the bile duct was

made. Cutaneous tuberous and plain xanthomata developed in both about one year after the jaundice was first noticed. It may be emphasized that chronic jaundice in the usual biliary cirrhosis is not accompanied by the formation of xanthomata even after a very long period of jaundice. In cases of ordinary biliary cirrhosis the cholesterol in the serum may be high and in cases of biliary cirrhosis with partial obstruction it may be very high, but no xanthomata develop. The appearance of xanthomata during a prolonged jaundice suggests a special type of hepatic cirrhosis and bile duct involvement. These are histologically identical with xanthoma cell formation in the skin.

The total cholesterol in the serum of both patients was high and the ratio of cholesterol to cholesterol esters was inversed. We attribute this inversion to the severe damage of the hepatic tissue. The phospholipids in the serum of both cases were not examined. We would expect in such a severe liver disease, in the light of experience gained from the separate determination of diaminophosphatide (sphingomyelin) and monoaminophosphatide (lecithin-cephalin), a low normal sphingomyelin but high lecithin and cephalin values.

A very intensive eruption of papulo-pustular xanthomata was seen in all of these three cases. The eruptive form of xanthomata changes in degree during the disease, because this form depends, in our experience, to a great extent on the cholesteremia.

The patient (Case 15), a young woman of 32 years, died of coronary thrombosis. Although an autopsy was not done, it seems very likely that the coronary thrombosis in this case was due to the same etiology which caused the xanthomata of the skin, liver and bile duct. Especially since we learned from the cases reported in the literature that juvenile patients who exhibited xanthomata of the skin and tendon sheaths died suddenly from heart disease and autopsy revealed severe xanthomata formation on the valves, large vessels and coronaries.

The third reported patient (Case 16), is alive and under our observation. She differs from the two other patients in two points. First, she is not constantly jaundiced. At times she has a slight yellowish tinge to the sclerae, sometimes a real jaundice, and other times, as at present no trace of jaundice. Secondly, three years after the onset of symptoms, she had only small xanthomata of the skin of both eyelids. However, the main symptoms in the three cases are chronic enlargement of the liver and spleen, constantly high cholesterol values in the serum, and independent of the jaundice, itching eruption of nodular pustular xanthomata.

It is astonishing that this form of xanthomatous disease of skin and liver with xanthomatous cholangitis is almost unknown, because it is never considered in the modern textbooks on medicine. Yet this peculiar complex of symptoms and its underlying pathology have been described by classical authors. We find it stated in some articles that Rayer in 1835 [97] de-

scribed "plaques jaunâtres des paupières" and that Addison and Gull in 1850 [1] named the same disease "vitiligoidea planum et tuberosum." But nowhere in the modern literature are Addison and Gull credited with the full description of the symptom complex of skin xanthomata with a peculiar form of cirrhosis of the liver although in fact these authors did describe three patients with jaundice, xanthomata of the skin and hepatic cirrhosis in Guy's Hospital Reports, 1850. From the same hospital, Fagge,[36] Howes,[36] Murchison [79] and Pye-Smith [94, 95] report similar cases in the Transactions of the Pathological Society with detailed autopsy findings and histological examinations. In the French literature Bazin,[12] Hillariet,[12] Chambard,[12] in 1878 report similar cases with xanthomata and jaundice. Besnier [16] in 1876 describes tuberous xanthomata and plaques with liver, heart and arterial disease.

The clinical description of Addison and Gull in 1850 [1] is so important that one of the reported cases may be quoted verbatim to demonstrate the similarity to one of our reported patients (Case 15).

"Case of Eliza Parachute, aged 33, of middle stature, moderately well nourished; mother of six children; catamenia regular. Her present illness began in 1848; she attributes it to fright, and to a blow received in the left groin whilst attempting to separate two men who were fighting. Two days after this she became jaundiced, and had from time to time severe paroxysmal pains about the hypochondria, lasting for a day or two; the liver being also enlarged and tender. Four months after the commencement of the jaundice (August 4, 1848) she was admitted into the Hospital under the care of Dr. Hughes. She remained in until September 26, and left much in the same state she was in when admitted. There was at this time nothing complained of beyond itching and irritation of the skin common in jaundice. The present affection began after the jaundice had continued 14 months, when she again came under the care. It first appeared in the hands, spreading across the flexures of the joints of the fingers and palms. Soon afterwards a yellowish patch of discoloration began near the inner canthus of the eyelid, and then a precisely symmetrical one at the same part on the opposite eyelid. These patches are very slightly raised, and not obviously indurated; they have extended very slowly. At this time the patches on the face existed as above described. Along the ridges bounding the flexures in the palm and about the joints of the fingers, there were yellowish, opaque, irregular, and somewhat raised lines. About the thumb, first joints of the fingers, and inner interior parts of the wrists, there is a gradual transition to a tubercular prominence of the affected parts, and some distinct tubercles exist on the elbow and knee."

In the same paper Addison and Gull [1] gave the first description of the eruptive form of xanthomata diabeticorum in a diabetic patient, in a wonderfully picturesque manner. The pupils of Addison at the Guy's Hospital report the first anatomical findings in the liver, bile ducts and arteries. Moxen (Trans. Path. Soc., 1873) [78] reports the case of a man 32 years of age, severely jaundiced for two years with two attacks of colic; xanthelasma on the palms, scrotum, back, ears, cheeks and lids. He died of hemorrhage from a hepatic lesion. The postmortem examination showed only hepatic cirrhosis, no gall stones.

"The gall ducts throughout the organ were excessively wide so that on section of the liver their contents welled up in enormous quantity, being a white clear fluid, in strong contrast with the serum of the blood which was golden yellow. These dilated gall ducts had xanthelasma looking patches within them—that is, white opaque patches. The hepatic duct at the point of union of its two divisions was swollen from the pressure in it of a firm, tough matter making a little soft knot of the size of an almond around it and in its walls. The microscope showed only fibrous scar tissue in the thickening."

This is like the operative finding in our Case 14. Similar reports are found in the literature (Futcher,[41] Weidman[150]). The scar tissue in all these cases, which almost completely occluded one of the bile ducts, is granulomatous in character resulting from xanthomata patches lining the wall of the bile duct. Xanthomatous patches were found on the arteries, especially the aorta, on the trachea near the bifurcation, and one in the capsule of the small spleen. Hilton Fagge[86] reported in the same volume of the Transactions (1873, v, 242) a case of vitiligo (which has since received from Erasmus Wilson the more euphonious title of xanthelasma) with a pathological report by Dr. Howse. The patient was jaundiced for seven years continuously. Xanthomatous patches were found on the eyelids, hands, abdomen, lips, larynx and trachea; hepatic cirrhosis, enlarged spleen with a large number of minute white grains within it. The lungs and brain were normal. The left auricle, aorta and pulmonary artery and almost all the vessels presented a large number of yellow spots and patches.

"They were sharply defined and raised slightly above the level of the lining membrane of the vessel." "The nature of the growth appears to be essentially the same wherever it occurs, whether in the mucous membrane, on the tendons or on the skin. It appears to be a kind of universal atheromatous change. From wherever the sections are taken they show fine granular cells variously disposed amongst the fibrous tissue of the part affected. In the other growths they undergo still further degenerative changes becoming converted into lumps of calcareous matter, crystalline bodies, etc. Thus it would be a matter of indifference whether we should speak of the cutaneous disease as an atheroma of the skin or of the arterial affection as a xanthelasma of the aorta."

A third case with autopsy was described by a third physician of Guy's Hospital, Pye-Smith, at the same time,[94] in the Transactions of the Pathological Society 1873, p. 250. A woman 49 years of age had attacks of colic over a period of two years with intermittent jaundice but her urine was always dark. She showed xanthelasma only on both eyelids. She died of an intercurrent severe erysipelas. The postmortem examination revealed only one calculus in the gall-bladder but the biliary ducts were found to be much dilated. "Patches precisely like those in the eyelids and hands were found on the surface of the spleen and in the mucous membrane of the dilated hepatic ducts." The liver showed a slight degree of interstitial cirrhosis. "The patches in the ducts looked just like atheroma in the artery with which condition indeed, they correspond histologically."

Already in 1882, 23 similar cases with jaundice and xanthelasma were

collected and described by an English Committee for investigation of xanthomata (J. Hutchinson, A. Sangster and H. R. Crocker [54]). The question that xanthomata exist without liver disease was decided by the report of cases of xanthomata plana and tuberosa without jaundice. In 1884, Balzer,[10] referring to three patients with liver disease and xanthomata in the French literature, believed that he proved an infectious etiology of the disease but this was never confirmed. In 1889 Hardaway [49] speaks of xanthomatous diathesis in a case to which we shall refer later. He also suggested that xanthomata is a "diathesis" and that its connection with hepatic disarrangement was entirely secondary, or in other words, that jaundice occurring during the course of the disease was a consequence of a deposition of xanthomatous tubercles in the "liver." This wise conception was not accepted and P. Weber in 1903 [148] as well as Futcher in 1905,[41] reporting three cases from Osler's wards at Johns Hopkins, believed that chronic obstruction of the bile duct is the primary cause of the development of the xanthomata. This opinion of Futcher is surprising because he describes "that on section of the liver the bile ducts stood out everywhere looking like sclerotic arteries. The walls of the bile ducts are considerably hypertrophied containing elastic fibers and the lumina are lined with a mass of lymphoid and planum cells similar to those already described in the skin lesion." Posner, in 1909,[92] describes a patient with bile duct obstruction who was operated upon but no obstruction found. Xanthomata of the skin developed after the operation. Hepatic cirrhosis and all kinds of xanthomatous changes in the organs were found at autopsy. In 1900 Chvostek [32] pointed out that "jaundice and xanthelasma" are the result of the same disease, namely they are due to a xanthomatous involvement of the liver which results in cirrhosis of this organ and to a xanthomatous involvement of the skin which is evident as xanthelasma."

S. C. Dyke, 1928,[34] in his paper on "Hypercholesteremic Splenomegaly" deals with the same disease—jaundice, xanthelasma planum and tuberosum, xanthomatous involvement of spleen and lymph nodes. Buerger [25] describes a female 55 years of age with extensive xanthomata tuberosa and plana, jaundice and hepatic cirrhosis with the extreme total cholesterol value of 2575 mg. per cent, 1444 mg. per cent free and 1131 mg. per cent esters. A similar case with 1020 mg. per cent total cholesterol is described by Weidman and Boston.[152] The autopsy findings in these cases showed biliary cirrhosis, xanthomata cells on the splenic and hepatic capsules, also on a scar of herpes zoster (like Hardaway's case) besides the extensive tuberous xanthomata of the skin. The most important feature of this paper is not the occasional finding of a polyp of questionable adenocarcinoma of the ampulla of Vater, but the photograph of the histological picture of the wall of the gall-bladder and the similarity of findings on the wall of the bile duct, both showing extensive xanthomatous changes and xanthomatous scar tissue. It was recognized that the common bile duct was enlarged to the size of an

average thumb and the head of the pancreas was indurated; however, a cause for the dilatation in the form of biliary obstruction could not be demonstrated. (Finding on laparotomy, immediately after which the patient died.)

### The Etiology of the Biliary Cirrhosis Found in Cases of Jaundice and Xanthelasma

Chvostek [32] showed for the first time that xanthoma cells and xanthomatous scar tissue are found in these cirrhotic livers.

Our Case 14 (already reported by Schilling) exhibited the same findings of xanthoma cells scattered throughout the liver as the case of Chvostek and the case reported by Weidman and Freeman in 1928.[149] It is evident that these nests of xanthomatous cells resulting in xanthomatosis of the liver undergo destruction sooner or later. The result is the development of connective scar tissue and cirrhotic changes of the liver. However, this process in the xanthomatous liver is not necessarily the main cause of the large cirrhotic liver of the biliary type of cirrhosis in all the described cases. The main clinical symptom of this disease, "jaundice of years duration," would not be explained by a simple cirrhotic process of the biliary type.

On the basis of an intensive study of the literature, and our experience, we believe that the xanthomatous changes on the walls of the larger bile ducts which are observed in almost all reported autopsies, and which give rise to the thickening as well as to the partial obstruction and dilatation of the bile ducts through the formation of xanthomatous scar tissue, are the cause of this peculiar biliary cirrhosis. We know that chronic inflammation of the bile ducts leads very often to biliary cirrhosis. Hence it seems reasonable that degenerative changes in the wall of the bile ducts due to xanthomata formation may also produce cirrhotic livers.

The name "xanthomatous biliary cirrhosis" with xanthomatosis of the bile ducts may therefore be ascribed to this form of cirrhosis. In naming this form of cirrhosis, first described by Addison and Gull in 1850, we would like to say that xanthomatous biliary cirrhosis is only one of the features of a systemic and usually hereditary disease which may involve different organs and produce different clinical pictures. We shall see later that there are two distinct groups of organs which may be affected by xanthomatous changes resulting in peculiar symptom complexes. However, xanthomatous changes may be observed isolated in one organ and, as in a few cases, involving almost every organ. The former conception that the cause of the development of xanthomata is due to biliary cirrhosis and jaundice resulting from obstruction of the common bile duct by stones, inflammatory changes or tumor, does not meet with the facts and our clinical experience.

Xanthomatous biliary cirrhosis due to xanthomatous involvement of the bile ducts shows in some instances nests of xanthomatous cells in small

areas of the liver tissue itself and in the spleen described as saffron yellow spots of pinhead size. These little xanthomata in the liver and spleen as well as in the capsule of the liver and spleen do not result in those extensive cirrhotic changes above described as " xanthomatous biliary cirrhosis " although they may be found in the same livers together with the xanthomatous involvement of the bile ducts.

On the other hand, the development of larger areas of xanthoma cells in the liver and especially in the spleen is described without jaundice and without cirrhosis but with enlargement of liver and spleen. In these cases of hepatosplenomegaly a high grade of lipemia was primarily observed. In 1931 Buerger and Grütz [23, 24] describe such a patient, a boy of eleven years of age with a large liver and spleen; 9476 mg. per cent of fat, 686 mg. per cent total cholesterol, 310 mg. per cent free and 376 mg. per cent ester cholesterol. This boy was not jaundiced but there were xanthomata on the face, neck, arms and buttocks; also xanthomata in the mucosa of the mouth and in the larynx. Buerger and Grütz [23, 24] report that the skin manifestations, in contrast to the findings of xanthomata tuberosa, did not show true xanthomatous tissue but only a few xanthoma cells. We would suggest that these nodules belong to the eruptive group of nodular papular xanthomata which come and disappear as described in our Cases 14, 15, 16 and as in severe lipemia in the diabetic Cases 21 and 22. Buerger and Grütz have not published up to now the further development of histological lesions in this unusual case but we agree with them that this case is different from the cases with jaundice and xanthelasma due to " xanthomatous biliary cirrhosis." The anatomical findings in liver and spleen of the " hepatosplenomegalic type without jaundice " may be similar to the findings of Lubarsch [66] in 1918, and Bross [22] in 1920 in a case of xanthomatosis and diabetes mellitus with high grade lipemia where the enlarged liver and spleen as well as all lymph glands were filled with xanthoma cells. The case of Lubarsch-Bross forms a transition to a group to be presented later as " secondary xanthomatous diseases " with xanthoma cell formation in spleen and liver in diabetic lipemia. This condition was first described by Schultze [121] in 1912 as " lipoid cell hyperplasia of the spleen."

*Chemical Findings.* In our three cases, as in all cases of xanthomatous biliary cirrhosis in the literature where cholesterol determinations were made, there is high total cholesterol and in advanced cases of cirrhosis an inversed ratio of cholesterol : cholesterol esters. High total cholesterol is in conformity with biliary stasis while inverse cholesterol : cholesterol ester ratio indicates severe liver damage according to Thannhauser and Schaber and many others. The bilirubin of the serum is high and shows a direct and indirect reaction because in this kind of cirrhosis as in other biliary cirrhoses, bile stasis and liver damage is the underlying pathological condition.

Only Case 16, the lightest case of the three reported, was examined by our method to determine the monoamino- and diaminophosphatides. As

in the cases of cirrhosis the total phospholipids are high, the determination of lecithin (monoaminophosphatide) and sphingomyelin (diaminophosphatide) shows that the increase of total phospholipids in the serum is due only to an increase of monoaminophosphatide while sphingomyelin (diaminophosphatide) is normal or even diminished; a characteristic finding for all xanthomatous tissue, while in Niemann-Pick's disease the diaminophosphatide (sphingomyelin) is found excessively increased.

*Diagnostic Considerations.* The outstanding triad of symptoms in xanthomatous biliary cirrhosis is (1) enlarged liver and spleen with jaundice of years duration, (2) skin manifestations exhibiting tuberous and plain xanthomata of the elbows, knees, extensor surfaces of the extremities and buttocks, (3) hypercholesteremia with an inverse ratio of cholesterol: cholesterol esters. The jaundice may be intermittent in character as in Case 16, but the liver and spleen remain enlarged and hypercholesteremia is always found, even during the time the patient does not show distinct jaundice. The skin xanthomata usually develop after the jaundice but in rare cases of tendon sheath xanthomata the xanthomatous biliary cirrhosis may develop in a later period of life. (Case 1 shows an inverse ratio of cholesterol: cholesterol esters.) On the other hand, the xanthomata may develop very late as in Case 16. We are inclined to believe that the eruptive form of xanthomata (papulo-pustular form) may have been present in other cases reported in the literature, but the connection with the disease (that is with the hypercholesteremia) was not recognized. We would like to emphasize that this extremely itchy eruptive form which comes and goes is an aid to the early recognition of the disease.

## Correlated Features of Xanthomatosis of the Normocholesteremic Type

It is important to point out that certain features of xanthomatosis are found together. They are: (1) xanthomata tuberosa and plana of the skin, (2) tendon xanthomata, (3) xanthomata formation on the endocardium and on the intima of blood vessels, (4) xanthomatous biliary cirrhosis and xanthomata formation in the liver and spleen. This group of xanthomata exhibit hypercholesteremia, high monoaminophosphatides, and high fat in the serum as well as in the tissues. The second group of xanthomatous diseases exhibit on the skin, if there is any skin involvement, most peculiar and for this group, characteristic universal lesions which are in localization, color and size, entirely different from xanthomata tuberosa and plana. This kind of xanthomata disseminata is associated with diabetes insipidus, involvement of the brain and nerve tissue, bones, lungs and lymph nodes. In contrast to the former group normal cholesterol or high normal cholesterol in the serum is the rule in this group.

I am very much indebted to Dr. P. A. O'Leary, Dr. H. Montgomery and Dr. A. E. Osterberg, Mayo Clinic, Rochester, Minnesota, for the permission to use Case 17 and Case 18 for publication in this paper.

## Xanthomata Disseminata

*Case 17.* S. S., a man, aged 42 (1932) first seen in June 1927, had noticed increased thirst and polyuria in November 1925. He would drink about 20 glasses of water during the day and would wake up at night because he was thirsty. He could not remember any illness or other incident which might have brought on the condition. About the same time he noticed yellowish-brown elevated areas on the skin of the antecubital fossae. It seems probable that the appearance of these lesions antedated the onset of the diabetes insipidus but that they were not striking enough to attract the patient's attention for some time. Similar soft tumor-like nodules presently appeared in both axillae and on the sides of the neck, and smaller, paler plaques under the eyes. At his first visit, general examination was essentially negative except for the lesions on the skin in the areas mentioned. He was found to be passing not more than 2000 c.c. of urine daily and his oral fluid intake was recorded as not more than 2200 c.c. The specific gravity of the urine varied from 1.006 to 1.012. Roentgenograms of the sella turcica were negative. The blood sugar was 0.10 per cent; the basal metabolic rate was normal, plus 3 per cent. A biopsy made from one of the nodules in the axilla revealed the typical picture of xanthoma.

The patient returned to the Mayo Clinic in January 1932, showing marked increase in the number and extent of xanthomatous lesions as compared with the status shown by photographs taken at the time of his previous visit. The progression had been so gradual, however, that he could not say whether they were still increasing or were stationary. About two years before this last visit, xanthomatous nodules had appeared around the anus and had been excised because of itching. They had recurred in an area of larger radius, and the itching associated with them formed his chief complaint. His thirst and polyuria were of less degree, he thought, than on his former visit. He had tried hypodermic injections of solution of pituitary in 1927 and had found that they controlled his thirst, but he had not experienced sufficient discomfort to continue the use of the drug.

Examination disclosed large areas of soft, confluent bronze-colored nodules in each axilla (figure 23). There were smaller areas in each antecubital fossa, where the nodules were pinkish-brown; some of these tumors were slightly pedunculated and as large as 2 by 1 by 1 cm. There were numerous smaller flat nodules on the neck, face, groins, and sides of the abdomen. Around the anus for a radius of from 6 to 7 cm. the skin appeared smooth, gray and thick, perhaps owing in part to previous excision of nodules; at the periphery of this area were soft, sessile, pinkish tumors like those in the hollows of the elbows. A continuous ridge of nodules ran along the median raphe to the scrotum, where it ended in several nodular enlargements. Again, it was interesting to note that there were no lesions on the elbows, knees or surfaces subject to trauma. In the mucous membrane of the mouth there appeared five yellowish areas, one on the left margin of the tongue, one in each cheek, one in the left lower jaw and one in the uvula. There was no involvement of the posterior pharyngeal wall or scarring, as was present in Case 1. There were eight areas visible in the larynx and upper part of the trachea where the mucous membrane was similarly involved. As far as one could see down the trachea, the same condition was present. There was no scarring in the larynx or trachea and no embarrassment of respiration. On the upper part of each cornea covering the upper margin of the iris, was a yellow, slightly elevated mass resembling so closely some of the other nodules, particularly those in the mouth, that there seemed no reasonable doubt of their identical nature. Biopsy was made from a nodule on the arm and again revealed typical xanthoma, not differing essentially from the picture seen five years before in tissue from the same patient nor from that seen in sections made from the first patient (Case 1).

General examination was essentially negative except for the lesions described. The output of urine was between two and three liters daily; the specific gravity was

1.010; urinalysis was negative. The concentration of hemoglobin was 10.8 gm. (64 per cent); erythrocytes numbered 3.5 million per cu. mm. and leukocytes 11,700. Serologic tests for syphilis were negative. Roentgenograms of the thorax and sella turcica were negative. The eyegrounds were essentially normal. Analysis of the

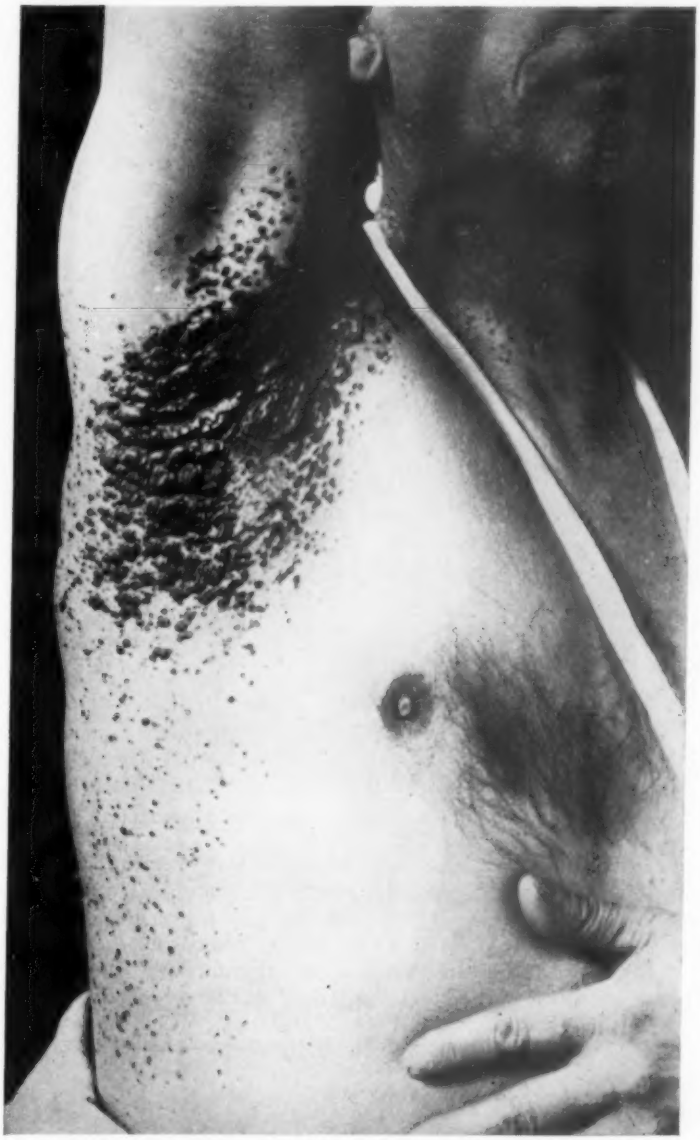


FIG. 23. Case 17. Xanthomata disseminata.

chemical constituents of the blood gave these figures: cholesterol 167 mg., cholesterol esters 119 mg.; total phospholipids 246 mg.; fats as fatty acids 273 mg. One nodule was excised and the analysis of the dry tissue as follows: total cholesterol 4.55 mg. per cent; cholesterol esters 3.66 mg. per cent; fatty acids 3.64 per cent.

Treatment was begun as in the other case. Roentgen-ray exposures were made over the region of the sella turcica, both sides of the neck, and over the right arm. A diet low in calories and low in fat was tried. There was no improvement during the period that the patient remained under observation.

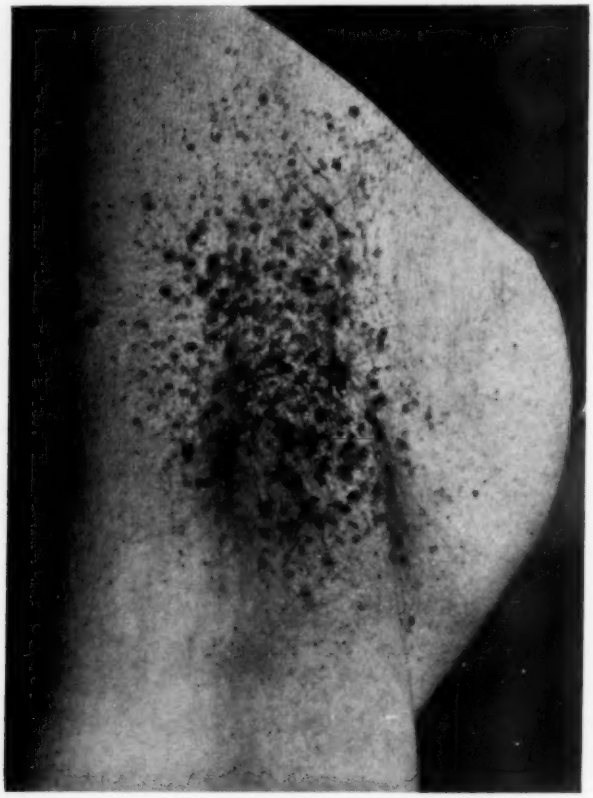


FIG. 24. Case 18. Xanthomata disseminata in the axilla.

*Case 18.* Mrs. H. A., married, aged 48 years, was examined at the Mayo Clinic in June 1936, because of polydipsia. In June 1935, she noticed small red and yellow lumps under the arms (figure 24) and in the groin which increased in spite of roentgen-ray treatment. In March 1936, many lesions developed on the eyelids (figure 25). Six months after the first onset of the cutaneous lesions (January 1936), she developed symptoms of diabetes insipidus, including marked polyuria and an

FIG. 25. Case 18. Xanthomata disseminata of the eyelids.

output of eight gallons of urine daily. Diabetes insipidus was controlled fairly well by the use of pituitrin and amidopyrin. Examination of the skin revealed red-brown nodules from the size of a pea to a pin, but none on the elbows, buttocks, knees and fingers. There were also lesions in the mouth. Blood chemical studies were as follows:

| Date | 6/26/36 | 7/9/36 |
|---|---|---|
| Total cholesterol | 214 mg. per 100 c.c. | 235 mg. per 100 c.c. plasma |
| Total fat as fatty acids | 302 | 250 |
| Total phospholipids | 305 | 269 |

The hemoglobin was 15.4 grams per 100 c.c. of blood, the erythrocytes numbered 4.9 million per cu. mm. and the leukocytes numbered 10,600. The differential count was as follows: lymphocytes 31.0, monocytes 4.5, neutrophiles 60.5, eosinophiles 2.5, and basophiles 1.5 per cent. The flocculation test for syphilis was negative. The urine showed specific gravity of 1.009. Roentgen-ray of the chest was negative. Roentgen-ray of the skull, including the sella, showed a benign frontal hyperostosis.

In February 1937, the patient returned. The skin lesions had become much more numerous in the axilla and groin, and there was marked, diffuse, reddish infiltration of the face over the area usually involved by rosacea, made up entirely of miliary xanthomata. There was involvement under the eyes, over the axillae, lower portions of the breast, abdomen, labia, and inner surfaces of the thighs, and a few lesions were present in the cubital fossae,—all this in spite of the fact that the diabetes insipidus appeared to be quite well controlled. (The liver was down about four fingers. The spleen was not palpable.) The patient was put on a low-cholesterol animal-fat-free diet. The chemical analyses of the blood were as follows:

| Date | 2/6/37 | 3/7/37 |
|---|---|---|
| Total phospholipids | 349 mg. per 100 c.c. | 297 mg. per 100 c.c. plasma |
| Total cholesterol | 273 | 231 |
| Fat as fatty acids | 514 | 405 |

At this time the erythrocytes were 4.6 million per cu. mm. and the leukocytes 8700. The urine showed a specific gravity of 1.007. There were xanthomata involving both cheeks, and the floor of the mouth. There were some suspicious areas on the margins of the tongue; both arytenoid regions showed definite yellowish nodular areas.

When the patient was examined May 10, 1937, she had been feeling well, and had been having very little trouble with thirst or polyuria. She had been taking three amidopyrine tablets at night and three injections of pituitrin a week. All the skin lesions were somewhat more extensive than in February. The blood analyses on May 12, 1937, were as follows:

| | |
|---|---|
| Total phospholipids | 260 mg. per 100 c.c. plasma |
| Total cholesterol | 208 |
| Cholesterol esters | 134 |
| Free cholesterol | 74 |
| Total fat as fatty acids | 290 |

The bilirubin was 1.0 mg. per cent—reaction indirect. (The liver was no longer palpable.)

*Comment and Discussion.* It is remarkable that this form of xanthomata, until the paper by Polano [91] (1936) and Montgomery [76] (1937) appeared, was confused with the other manifestations of xanthomata, although it differs in appearance, color, localization and size from the tuberous and flat form of skin xanthomata. Under the title "xanthoma multiplex molluscum lipoides" Virchow,[145] who was the first to describe xanthoma

disseminata, adds to his paper a colored lithograph. On this lithograph the characteristics of this kind of xanthomata can be seen. The localization is on the hollow of the knees and elbows, not on the extensor surface; the color is not ochre or carrot-like but the color of a lemon at first and later dark brown like mahogany, sometimes with a metallic shiny surface. Virchow's patient was first seen by the famous ophthalmologist, von Graefe, because he had a xanthomatous nodule on the cornea similar to other cases of xanthoma disseminatum described in the literature by Weidman and Freeman,[149] and our Case 17. Stephen MacKenzie [68] in 1882 described, under the title, "Two Cases of Congenital Xanthelasma," two brothers and one sister with this peculiar kind of skin xanthomata (disseminata) in such an expressive manner that the difference between other xanthomata of the skin is seen at once. We quote his original description verbatim:

"Samuel H., aged 45. The eruption consists of very slightly raised, soft smooth patches of a lemon or chamois leather color, arranged somewhat in ridges or lines. The patches are of irregular shape and size, none much larger than a pea, and some not much larger than a pin-head. In places, as in the neck and abdomen they are so closely packed together as to appear confluent, but on stretching the skin the patches are separated by furrows. The larger patches are of deeper color and well defined, but the smallest are of a very faint lemon tint, fading into the healthy skin. The color is deeper in the exposed parts (as in the neck) than in covered parts. The affected skin is elastic and pliable and can be readily pinched between the fingers. There is not and never has been any itching of the skin and the patient has never experienced any inconvenience from it.

"*Distribution:* None on eyelids (most of the patients show affection of this part) nor on any part of the face or scalp. The neck is markedly affected, a band of the yellow plaques extending round it like a collar. From the neck the eruption extends over the scapulae and clavicles slightly. Both axillae are affected and the patches extend down over the integument covering the coracobrachialis and the biceps muscles. The bend of each elbow is slightly affected. There are a few faintly marked patches in the skin over the lower margins of each pectoral muscle. The lower lateral parts of the abdomen, the pubes, base of penis and scrotum are slightly and the groins are markedly affected. In the popliteal spaces are quite well marked patches.

"His brother, Jonathan H., aged 47, and his sister present a condition of the skin identical in character with that described on the neck, axillae, bend of elbows, groins and popliteal spaces. The sister is older than her brothers and remembers the eruption on the brothers' and on her own skin as babies. They have never caused any disturbance of their health. Neither has suffered from jaundice. Their paternal grandfather had a similar affection of the skin."

The familial occurrence of tendon xanthomata is widely known; the familial occurrence of xanthomata disseminata is only described in these cases of MacKenzie.

In studying the literature, we found xanthomata disseminata described but not differentiated from other xanthomatous manifestations, by Virchow [145] (1871), Poensgen [90] (1883), Eichoff [35] (1884), Koebner [61] (1888), Tschistakow [140] (1891), Anderson [2] (1882), E. Rhodes [98] (1906). In an outstanding but not commonly known paper Pusey and Johnstone [93] (1908) describe an 18 year old boy with a xanthomatous skin lesion "of

the diabetic type," associated with diabetes insipidus. The patient voided five liters of urine daily; specific gravity 1.002 to 1.006. The xanthomata are easily recognized by their description and localization as xanthomata disseminata. The skin was covered with an eruption varying from the size of a pin-head to a millet seed. The color was reddish in the small papules to a glistening yellow or bronze in the larger ones, which were confluent. The nodules were also seen on the mucosa of the mouth, epiglottis and larynx, cornea and sclera. The patient had spells of dizziness and fainting, during which he asked for water. Two years later tracheotomy was performed in order to relieve laryngeal stenosis caused by xanthomata. Later the spells of dizziness disappeared, but the diabetes insipidus persisted. Pusey deserves credit for having first described the clinical syndrome consisting of a peculiar form of skin xanthomata "intermediate form clinically between xanthoma diabeticorum and xanthoma multiplex" and diabetes insipidus. This peculiar form is, however, xanthoma disseminata and diabetes insipidus. He did not report in his first communication [93] (1908), as is erroneously quoted, xanthomata of the skull. W. H. Siemens [122] describes, under the heading of xanthoma multiplex, what we believe to be xanthoma disseminata. Siemens, in collaboration with Rosenthal and Breunisch [99b] first recognized that there are xanthomatous skin manifestations which are associated with normal cholesterol values in the blood in contrast to xanthomata tuberosa and plana. The difference in the appearance and the type of xanthomata was not emphasized by the various authors because the histological findings were the same as in xanthomata tuberosa and plana, and also because no single man observed a sufficient number of cases. Spillman and Watrin [126] (1921) describe in the French literature a boy who had xanthomata disseminata (according to the published photograph and to the description and the localization of the skin lesion) and diabetes insipidus. Neither bone changes nor exophthalmus were found. Turner, Davidson, and White [141] (1925) indeed were the first who differentiated xanthomata disseminata from other xanthomatous eruptions. They reported and photographed a patient, who exhibited this characteristic kind of xanthomata. They describe the papules as 1 to 4 mm. in diameter, varying in color from golden yellow to chocolate brown, distributed all over the body; around the neck, axillae, down the arms, involving both flexor and extensor aspects, eyes, abdomen, epiglottis, lateral aspects of the thighs and buttocks. The lesions of the mouth, pharynx, glottis, epiglottis, larynx and bronchi, as shown in the pictures, are unique in their extensiveness. The patient had an inspiratory and expiratory wheeze and the stenosis was so threatening that a tracheotomy had to be made as in Pusey's case.*

*Urbach (1928) [142] describes a new manifestation of xanthomatosis with the name "lipoid proteinosis." The chief clinical manifestation is severe hoarseness. In the developed disease all cases present fairly hard, yellowish-white infiltrations of the inner surface of the lips, soft palate, fauces, uvula or under surface of the tongue. There are also some scar-like depressions. The larynx is similarly and severely involved. Two forms of the lesions are distinguished: (1) nodular and (2) hyperkeratotic lesions.

The clinical identity of these cases with those of Pusey and Johnstone, 1908,[93] Turner,

This patient, like Pusey's, had diabetes insipidus for three years, the onset of which coincided with that of the skin manifestations. Death occurred. The postmortem findings were very important because they showed for the first time that xanthomatous tissue may develop in the lung and pleura and produce a severe fibrosis of the lung. Roentgen-rays of the lungs were not taken, so that the very impressive picture of diffuse little nodules simulating miliary tuberculosis, but consisting of xanthomatous tissue, was missed during life. It is very important to note that the autopsy which showed xanthomatous plaques on the mucosa of the stomach did not show any involvement of the liver, of the vessels, or of the heart. The examination of the brain showed conglomerate xanthomata cells in the pituitary and the tuber cinereum. Unfortunately the bones were not examined. Pusey and Johnstone's [93] patient and that of Turner, Davidson and White [141] were the first in whom the triad (1) xanthomata disseminata, (2) diabetes insipidus (brain involvement) and (3) xanthomatous disease of the pulmonary tissue was observed. Involvement of the bones has not been found; probably this was not looked for. In both cases there were neither xanthomata plana nor tendon sheath xanthomata, nor involvement of the blood vessels, bile ducts or liver. Blood sterols were normal in contrast to the reported cases in the other groups of xanthomata.

Recently Horsfall and Smith (1935) [53] reported under the title, "Lipoid Granulomatosis; Defects in the Bones; Exophthalmos and Diabetes Insipidus," a case with the complete clinical symptom complex of the group of xanthomatous diseases with normal cholesterol. The patient exhibited, according to the published photographs, typical xanthomata disseminata all over the body. The autopsy showed xanthomatous involvement of bones, lungs, dura of the brain, pituitary and spinal cord, lymph glands and spleen. Tendons, liver, bile ducts, and vessels were free, and xanthomata of the tuberous or flat form were not found. The cholesterol of the blood was normal.

K. Hoefer [52] describes a seven year old boy with xanthomata disseminata. In this case xanthomata disseminata were combined with diabetes insipidus but this patient had in addition to these symptoms, exophthalmos and characteristic skull defects as described by Hand, Schueller and Christian.

Hermann and Nathan [50] describe a patient with xanthomata disseminata and normal cholesterol in the blood. The lungs and bones were not examined. Diabetes insipidus was not present.

In 1931 Finney [37] reported a case of typical xanthomata disseminata

Davidson and White, 1925,[141] and Finney, 1931,[37, 38] is obvious. The photographs and colored pictures of the mouth and larynx published by Urbach are completely like the pictures of the case of Turner, Davidson and White. The skin manifestations of the "lipoid proteinosis" described by Urbach,[142] simultaneously with the lesions of mouth and larynx, are characterized by numerous pinhead-sized lesions grouped in mulberry-like, warty clusters. These lesions are, in view of size, appearance, localization and color (brown-violet sepia) identical with the lesions described first by Virchow 1871,[145] MacKenzie 1882,[68] and by different authors and are classified according to Polano,[91] Montgomery and Osterberg [76] as "xanthomata disseminata."

situated on the eyelids, neck, axillae, groin and scrotum; some of the tumors were pedunculated (described as molluscum by Virchow). The mucous membranes of the mouth and larynx were involved. The scarring of the larynx was "rhinoscleroma-like." The histological characteristics of these small xanthomata were the same as are seen in xanthomata plana and tuberosa: xanthoma cells, chronic inflammatory and scar tissue. This patient developed, one year after the onset of xanthomata disseminata, symptoms of diabetes insipidus with a daily urine output of six liters. The cases of Finney, Montgomery and New,[38] Weidman and Schaffer,[151] Montgomery and Osterberg,[76] show that diabetes insipidus and xanthomata disseminata may occur without bone and lung involvement. The case of Weidman and Schaffer showed as a peculiar feature in the postmortem examination a xanthomatous involvement of the pons; this was also found in the case of Chiari.[29, 30] The involvement of the brain is not confined to the pituitary or the tuber cinereum as found in the patient presented by Weidman and Freeman.[149] We shall discuss this later under a third group of patients.

It is evident that we have to deal with two clinical symptom complexes of xanthomatous diseases. These are to be distinguished by the kind of xanthomata exhibited on the skin, the organs involved and by the cholesterol figures found in the serum. The one group consists of cases showing xanthomata tuberosa and plana, tendon sheath xanthomata, xanthomatous biliary cirrhosis with xanthomatosis of the bile ducts. The other group shows disseminate xanthomata on the skin, xanthomatous involvement of the bones, skull, dura, brain (diabetes insipidus), scattered nests of xanthomata cells in the liver, spleen and lymph nodes without jaundice, but neither xanthomatosis of the bile ducts with xanthomatous biliary cirrhosis nor involvement of the tendons, intima of blood vessels or endocardium. The kind of xanthomatous skin manifestations permits us to predict which visceral organs may be involved at the same time. For this reason it is highly important to distinguish xanthomata disseminata from xanthomata tuberosa and plana as well as from the papulo-pustular eruptive form. Even in the painstaking paper of Rowland [100, 101, 102] we find his description of xanthoma disseminata mixed up with the description of the papulo-pustular eruptive form which may be present in hypercholesteremic conditions (diabetes mellitus and xanthomatous biliary cirrhosis).

Returning to Cases 17 and 18, it is evident that both belong to the second group of xanthomatous diseases (with normal cholesterol). Xanthomata disseminata and diabetes insipidus were the only features of this group observed in these cases. According to our discussion of the literature, the xanthomatous manifestations in this group may be limited to these two symptoms, or they may involve other parts of the brain, the bones and the lungs.

Histological findings: In the photomicrograph of Case 17, larger groups of xanthoma cells are seen directly under the epidermis (figure 26). In

other xanthomata of the disseminata type the number of xanthoma cells is smaller; in older nodules xanthoma cells are not found at all.

Chemical findings (Cases 17 and 18): The cholesterol content of the blood in these patients was a high normal; in fact in Case 18 the first de-

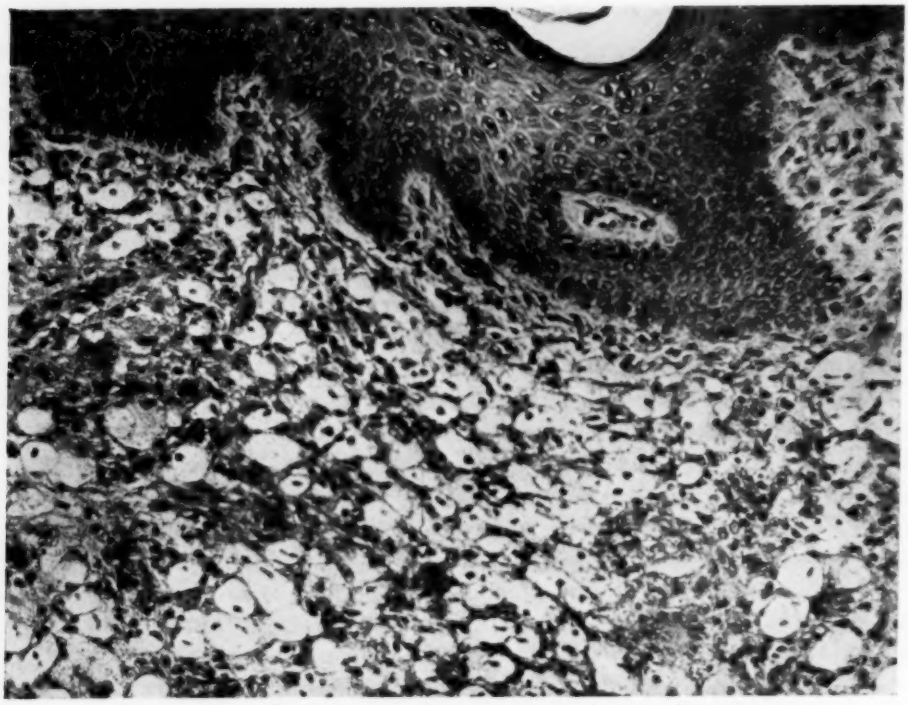


FIG. 26. Case 17. Histological picture of xanthomata disseminata.

termination was slightly increased but not as high as in the group of cases with xanthomata tuberosa and plana. In these cases only the total phospholipids were examined and not differentiated as monoaminophosphatides and diaminophosphatides. The low value of total phospholipids in Case 18 demonstrates also that this case belongs to the group of the normocholesteremic type. An organ analysis was not done because of the small size of the individual lesions. The significance of a normal content of cholesterol and phospholipids in the blood for the mechanism of the disease will be discussed later. At this point, however, we should like to emphasize that we do not believe that the two groups are different diseases although they are clinically different in regard to the organs involved and chemically different in regard to the cholesterol-phospholipid content of the serum. The two groups represent different features depending on the organs involved, but the anatomical changes characterized by xanthoma cell formation are the same.

## Osseous Xanthomata

*Case 19.* C. S., a 51-year-old Italian carpenter, noticed multiple excrescences developing in the region of his right ear and at the external canthus of his right eye when he was 35 years old. There was sero-hemorrhagic discharge from the right and several years later from the left ear as well. At the age of 41 numerous soft

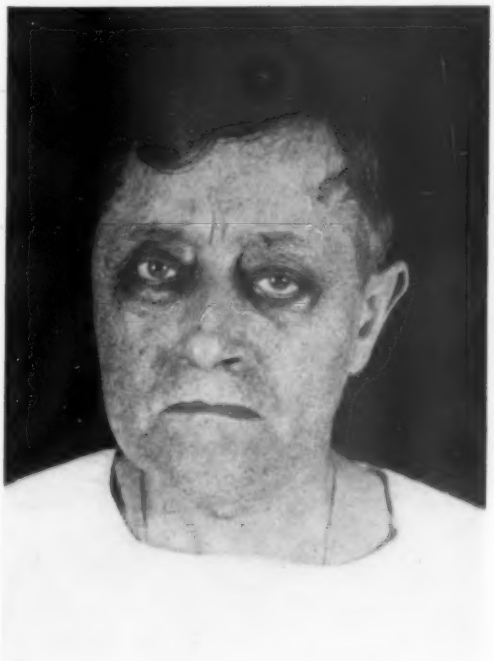


Fig. 27. Case 19. Deformity of the skull and of the orbits.

tender masses appeared on his head and drained sero-hemorrhagic fluid. Some of the older lesions ceased draining subsequently but other new ones appeared and drained. At about that time bilateral exophthalmos appeared and he began to suffer from polydipsia and polyuria (figures 27, 28). He was told at a hospital that his skull was paper-thin and that he had but three or four months more to live. He continued working, however, until at the age of 47 he fell down stairs and fractured his left femur and right humerus. In the Beth Israel Hospital, Boston, a plaster cast was applied and he was treated with irradiation by roentgen-rays. His fractures healed, the draining of the sinuses of his skull ceased and he was up and about, feeling well. His diabetes insipidus responded to a preparation of pitressin in oil. Fasting blood sugars were frequently elevated and a glucose tolerance test showed a diabetic type of curve. At no time was sugar present in his urine. His blood cholesterol values varied from 145 mg. per cent to 235 mg. per cent during his stay in the Beth Israel Hospital.

During the following years he developed a gradual unrecognized distention of the urinary bladder and became totally deaf. He knew of no member of his family with a similar condition or other manifestation of xanthomatosis.

We are indebted to Dr. J. D. Adams for referring this patient to us and to Dr. M. J. Schlesinger for permission to publish the histological slides.

On admission to the Diagnostic Hospital of the New England Medical Center January 9, 1937, he was slightly obese, not icteric, very thirsty and urinating at frequent intervals. His skull was strikingly deformed, showing a number of bulging areas and depressions which involved also the facial part of the head. The depressions were hole-like and funnel shaped; the surrounding bone was not thin, flexible or tender. None of these areas showed secretion. There was marked exophthalmos of both eyes. In the skin of both upper and lower lids, were several soft swellings, lighter and flatter than the xanthelasma (figure 29). His pupils were round, reacting to light and on accommodation; his fundi showed no abnormalities. Both ear canals

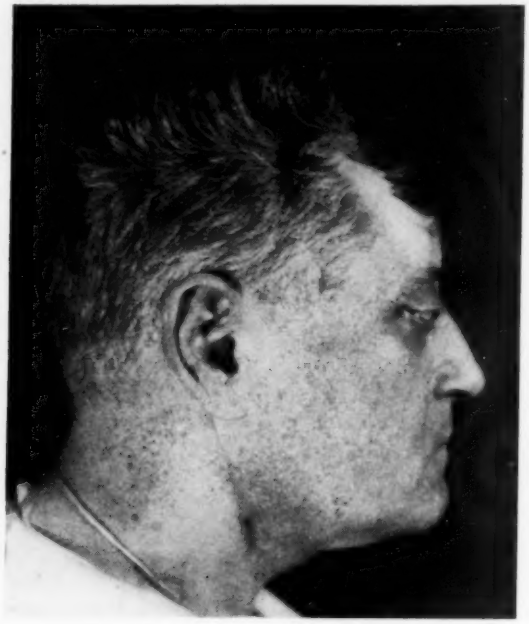


FIG. 28. Case 19. Exophthalmos.

were filled with soft, yellowish material which revealed no cholesterol crystals on microscopic examination. There was total nerve deafness. The mucous membranes of the mouth and throat showed no abnormalities. Heart and lungs were essentially normal. Blood pressure 160 systolic and 98 diastolic. In the lower abdomen the distended bladder extended above the umbilicus. After removal of 1000 c.c. of urine the bladder was still palpable above the symphysis. Liver and spleen were not palpable and not definitely enlarged on percussion. The right humerus and left femur were markedly deformed and shortened with limited motion in the right elbow and left knee joint. The skin of both hands was dry and hyperkeratotic. This condition was more marked over both lower legs where there were large, grayish-brown scales and onychogryphosis of the nails of both big toes. The thoracic spine was kyphotic and the patient's gait awkward, stiff and limping. He could walk only with the aid of a cane. No definite abnormalities of the central nervous system were demonstrated except the bilateral deafness, an occasional coarse tremor of the head and the *ischuria paradoxa*.

The volume of the urine varied from 4000 to 9600 c.c. daily. It contained from 36 to 75 grams of sugar daily. On a diet of carbohydrate 150 grams, protein 80 grams, and fat 100 grams, with 20 units of insulin twice daily, he remained sugar-

free. Under insulin treatment the urine volume diminished to between 1200 and 2500 c.c. daily.

Fasting blood sugar varied from 224 to 252 mg. per cent. The glucose tolerance curve was diabetic in type.

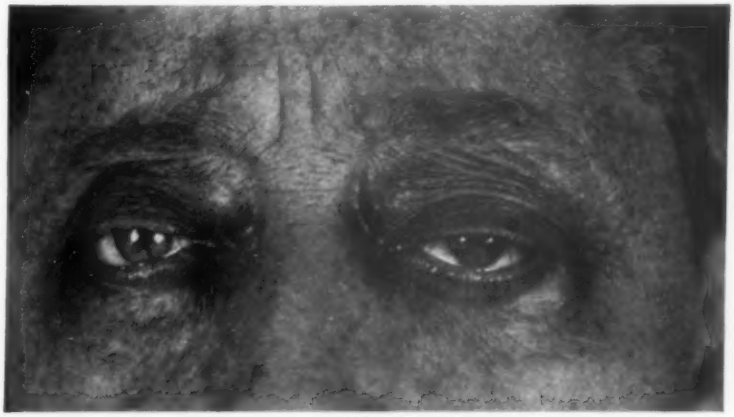


FIG. 29. Case 19. Xanthomata protruding from both orbits.

| | | |
|---|---|---|
| | Serum calcium | 10.5 mg. % |
| | " phosphorus | 4.3 mg. % |
| | Icteric index | 10 |
| | Phosphatase, 2.75 units in 100 c.c. serum | |
| 1/11/37 | Serum total cholesterol | 195 mg. % |
| | " free " | 67 |
| | " cholesterol esters | 128 |
| 2/3/37 | " total cholesterol | 200 mg. % |
| | " free " | 56 |
| | " cholesterol esters | 144 |

Basal metabolic rate minus 1 per cent.

Roentgen-rays of the skull (figure 30) showed what has been described as a geographical map, the tables of the skull being irregularly eroded in areas varying from pin-point size to large irregular-shaped defects. The sella turcica was not particularly enlarged. There was extreme increase in density at the base of the skull involving both mastoids, sphenoids and roofs of the orbits (figures 31, 32).

Roentgen-rays of the femora showed a few areas of decreased density in the head of the right femur, a large callous mass in the upper half of the left femur. There was a definite erosive lesion at the outer circumference of the right ilium, just above the head of the femur.

*Chemical findings of Case 19:* The cholesterol figures in this case show normal total cholesterol and normal cholesterol esters ratio in conformity with the figures reported in similar cases in the literature. In contrast to the normal cholesterol the total phospholipids are high. The individual determination of mono- and diaminophosphatides reveals that the increase of phospholipids is due to an increase of lecithin-cephalin fraction. The diaminophosphatides are low so that the ratio of diamino: monoaminophosphatides which usually varies from 1:0.5 to 1:1 reads 1:6.6. We found a similar abnormal ratio in another one of this group but we would not like to stress this finding at this time because the significance of low values of diaminophosphatides which led to this abnormal ratio is not known.

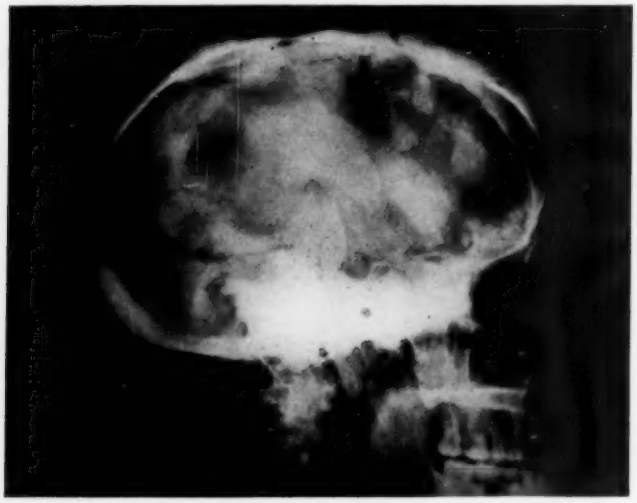


FIG. 30. Case 19. Skull roentgen-ray. Geographic skull.

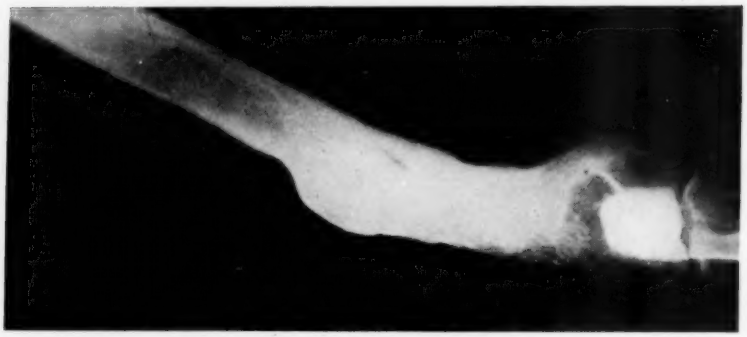


FIG. 31. Case 19. Roentgen-ray of the humerus, showing spontaneous fracture and xanthomatous cysts.

FIG. 32. Case 19. Roentgen-ray of the femur, showing spontaneous fractures and xanthomatous cysts.

*Histological findings of Case 19:* The xanthomatous tissues of the excised nodules of the dura contained more granulomatous tissue than do tuberous xanthomata of the skin. There were scattered xanthoma cells and conglomerate nests of cells in granulomatous tissue as shown in the photographs (figures 33, 34). Giant cells and

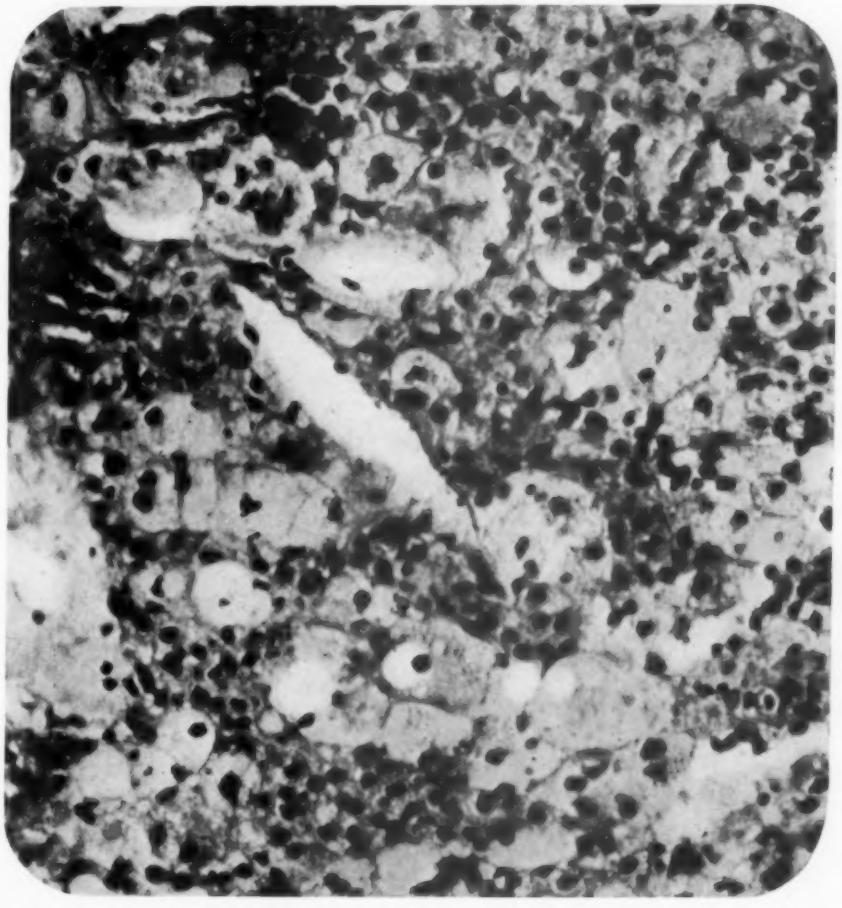


FIG. 33. Case 19. Histological picture showing the xanthoma cells of a xanthomatous nodule of the dura.

exudate cells were observed in the granulomatous nodules. There was no outstanding difference in the histological findings between the xanthomatous nodule of the dura and other xanthomatous tissue.

*Comment and Discussion.* There is no question but that this case belongs to the group of cases which were first described by Hand (1893),[47] Kay (1905),[58] Dietrich (1913),[33] Schueller (1915),[119] Christian (1919) [31] under different headings of bone diseases associated with diabetes insipidus. These authors did not recognize that this group of patients belongs to the group of xanthomatous diseases although Dietrich [33] called his case " fibro-

xanthoma." Rowland (1928) [101] deserves the credit of having proved conclusively (after reporting two of his own cases and discussing the others) that the defects in the membranous bones, the diabetes insipidus and the exophthalmos were due to xanthomatous changes in the bone marrow, to xanthomatous nodules of the dura and periosteum of the skull and orbit and to xanthomatous changes in the brain. The autopsy on one of Row-

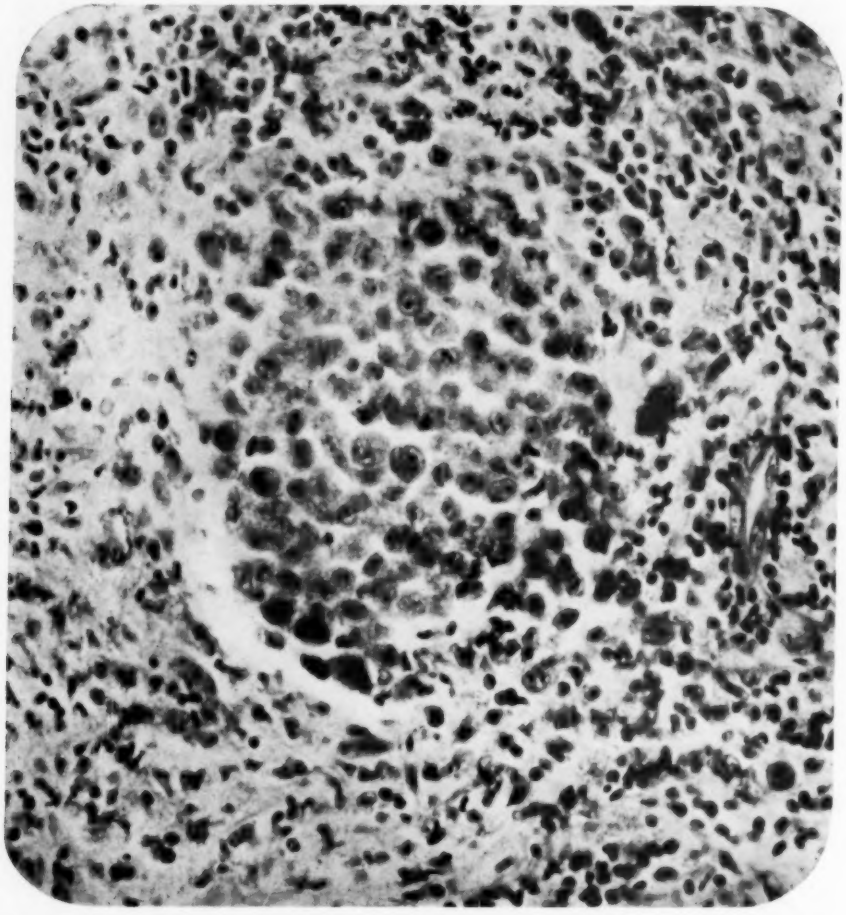


FIG. 34. Case 19. A nest of xanthoma cells in a xanthomatous nodule of the dura.

land's patients revealed these facts and showed that in addition to the bones, dura and brain, xanthomatous changes occurred in the lungs, pleura, lymph nodes and spleen.

We have reported above two cases (17 and 18) of xanthomata disseminata associated with diabetes insipidus. Similar cases in the literature show conclusively that xanthomata disseminata of the skin, xanthomatous changes in the brain (diabetes insipidus), xanthomatosis of the lungs,

lymph glands, spleen and bones belong to one group of xanthomatous disease. (To this group belong the cases of Pusey and Johnstone,[93] Spillman and Watrin,[126] Turner, Davidson and White,[141] Horsfall and Smith,[53] and K. Hoefer.[52])

The question arises as to whether the Hand-Schueller-Christian symptom complex is a special kind of xanthomatous disease or whether it should be included in the group of xanthomatous diseases characterized above as involving the skin (by xanthoma disseminata), the bones, the brain and dura, lungs, lymph nodes, and the spleen. It would appear that Hand-Schueller-Christian's disease clinically belongs to this group and is not an independent clinical entity. To justify this assumption we offer the following facts: (1) We find xanthomata disseminata occurring alone, with diabetes insipidus, with the Hand-Schueller-Christian syndrome, and with bone lesions (Hand,[47] Horsfall and Smith,[53] Pusey and Johnstone[93]); (2) xanthomata of the lungs occur with xanthomata disseminata, with bone lesions, with diabetes insipidus, and with Hand-Schueller-Christian syndrome (Turner, Davidson and White,[141] Rowland[101, 102]); (3) xanthomata disseminata alone or combined with diabetes insipidus, as well as the Hand-Schueller-Christian syndrome have a normal or high normal serum cholesterol.

The features of the Hand-Schueller-Christian syndrome which seem to separate it from the group are the lesions of the membranous bones and exophthalmos. The membranous bone lesions may occur, however, as a part of general osseous xanthoma without diabetes insipidus and without exophthalmos. Two cases of Fraser,[40] and our Case 20 (see below) illustrate this. The bone lesions as well as the exophthalmos have been shown by Rowland[101] and others, to be due to granuloma-like deposits of xanthomatous tissue formed by the same components as other xanthomata, namely, xanthoma cells, giant cells, exudate cells and granulomatous tissue. Exophthalmos and skull lesions are therefore the result of the same underlying anatomical substrate, as are all xanthomatous diseases. Rowland (1928)[101] collected 14 cases; Sossman (1932)[125] 45 cases (6 of his own) and Horsfall and Smith,[53] 50 cases of xanthomatous bone disease of the Hand-Schueller-Christian type. The number of cases would be decidedly higher if to these cases were added the patients with bone lesions and xanthomata disseminata with and without diabetes insipidus which belong to the same group.

The clinical features of our Case 19 do not differ essentially from the usual juvenile cases of the disease. The onset of the disease in this case at the age of 35 is, however, quite unusual, though there are already three cases of Hand-Schueller-Christian syndrome reported in patients over 40 years of age (Sossman,[125] Chester[28]). The usual age of onset in these patients is the first decade of life. The draining ear of our patient was due to xanthomatous involvement of the mastoid bone as is also observed in

juvenile cases. The enlargement of the bladder is probably due to failure of neurogenic control. The patient exhibited the symptoms of *ischuria paradoxa.* I had the opportunity to see another case of Hand-Schueller-Christian's syndrome with Dr. Blackfan of the Children's Hospital in Boston. This case, which is published by Dr. Sossman [125] as Case 3 in his series has also at present a distended bladder and symptoms of *ischuria paradoxa.* Disturbances of the bladder regulation are not reported in cases of diabetes insipidus. It seems likely that xanthomatous changes in the spinal cord may be present.

*Case 20.* S. S., a four-year-old female child. No family history of bone diseases. She began to limp and roentgen-rays were taken by her physician which revealed multiple bone lesions of the hyperparathyroid type. The child was sent to Dr. Fuller Albright at the Massachusetts General Hospital to whom I am indebted for the privilege of seeing the child with him and for permission to use the case for this paper. Her appearance was that of a normal four year old child. There were no signs of xanthomatosis of the skin; skull formation was normal; no exophthalmos; no diabetes insipidus.

| | | |
|---|---|---|
| Blood chemistry: | Serum calcium | 10.6 mg. % |
| | " phosphorus | 5.6 mg. % |
| | " phosphatase | 6.5 units |
| | " protein | 6.4 gm. % |
| Serum lipids: | Total cholesterol | 150 mg. % |
| | Free " | 40 |
| | Cholesterol esters | 110 |
| | Monoaminophosphatide (lecithin-cephalin) | 161 |
| | Diaminophosphatide (sphingomyelin) | 117 |
| | Total phospholipids | 278 |

Tissue (dried): Cholesterol content 2.07 mg. %

In contrast to the fact that the child was normal in appearance is the roentgen-ray report of her bones: "April 9, 1936: The skull, pelvis, femora, tibiae, left scapula, left ulna, right radius, both humeri, the right ninth and tenth and left sixth ribs show smooth sharply defined punched out areas of bone destruction (figures 35, 36). The most extensive changes are seen in the upper ends of the left femur and in the wings of the ilia. The head of the left femur is partially destroyed and the shaft of the left femur in the region of the trochanter and neck show multiple vacuolated areas of diminished density with smooth sharp dense margins. The lower end of the left femur and the upper end of the tibiae show irregular calcium deposits in lesions which may have been areas of destruction. There is a lesion in the left humerus at the junction of the middle and lower third which is quite unlike all the other lesions described. It is characterized by moth-eaten bone destruction and extensive periosteal proliferation along about 3 inches of the shaft on the lateral surface. No fracture is seen at this point and the soft tissues are normal. The bones show a slight degree of osteoporosis and their density is within normal limits except in the region of the lesions described.

"Comparing these films with those taken on May 28, 1934 shows definite increase in the number and size of the lesions. There has been apparent complete healing in a lesion at the upper end of the left humerus since 1934. It is probable that the lesions in the lower ends of the femora and tibiae are likewise healed but no previous films are available for comparison."

Tissue was obtained by biopsy from the bone marrow of the scapula. The amount

of cholesterol in this material is given above. The histological findings (figure 37) as reported by Dr. Granville Bennet of the Harvard Medical School are as follows: "The tissue is very vascular, being traversed by numerous thin-walled capillaries. In most areas there is little supporting tissue between capillaries. However, in a few areas there are larger amounts of connective tissue that indicate slight fibrosis of the bone marrow. The cytological picture of the tissue is greatly varied. Large col-

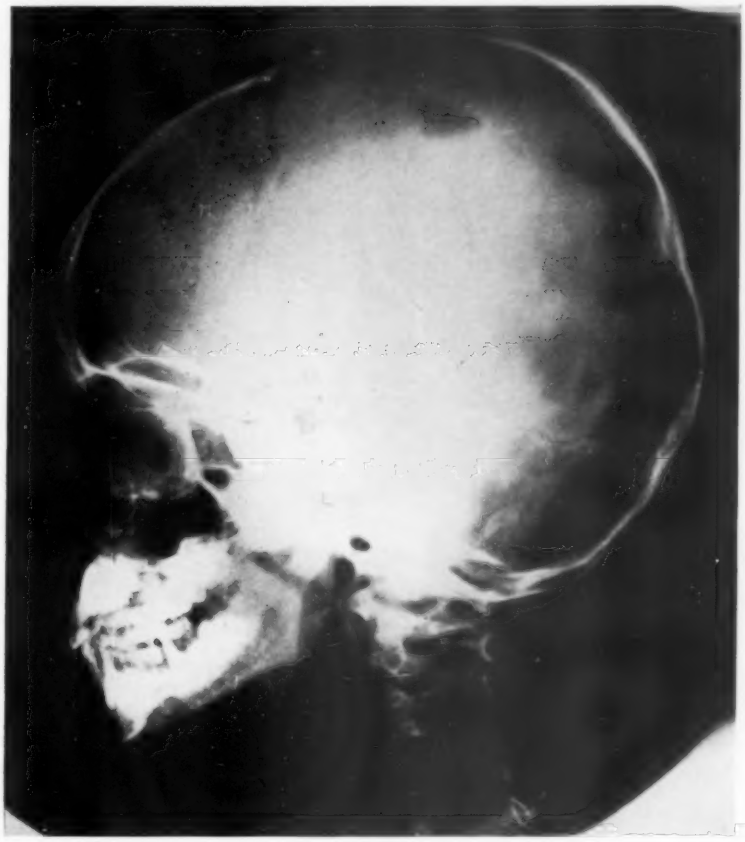


FIG. 35. Case 20. Roentgen-ray of the skull. Cystic xanthomatous bone lesions.

lections of bone marrow cells are observed in some areas. In other areas the hematopoietic cells are scattered in between good-sized collections of large mononuclear cells which appear definitely abnormal. These cells vary markedly in size and shape. The majority are oval or round. The cytoplasm is usually well stained with eosin dye. In many of the cells, however, the cytoplasm is finely vacuolated or contains brownish pigment, or in some instances it contains both pigment and finely divided vacuoles. The nuclei of the majority of these cells are oval or kidney shaped. Certain areas show marked accumulations of these cells. However, in the majority of fields such cells are scattered in small groups, through the marrow tissue.

"Frozen section stained with Scharlach R. show large accumulations of lipoid in finely divided globules. This material stains bright red.

"Sections stained with potassium ferrocyanide and dilute HCl show no recog-

nizable iron in the cells that contained brownish pigment in hematoxylin and eosin stained preparations."

Study of this material suggests that the skeletal defects were caused by accumulations of lipoid-containing cells and that the lesions represent one form of skeletal xanthomatosis.

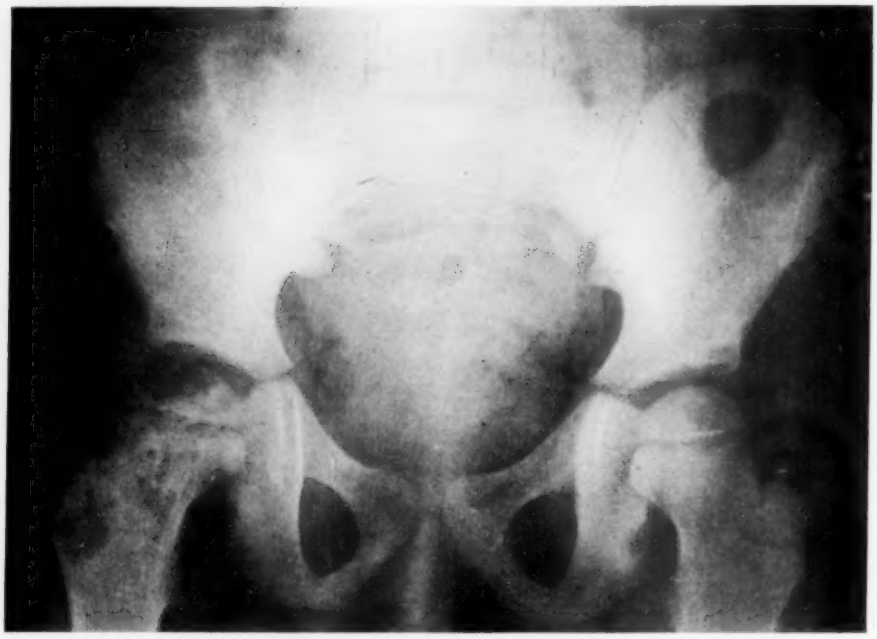


FIG. 36. Case 20. Roentgen-ray of pelvis. Xanthomatous cystic bone lesions.

*Comment and Discussion.* Case 20 shows xanthomatous involvement of the osseous apparatus only, skull, scapula, ribs, pelvis and extremities. There was no diabetes insipidus and no exophthalmos. The skin was always normal, with no evidence of xanthomata disseminata. The differential diagnosis from multiple myeloma was, therefore, difficult and was only possible by biopsy, which revealed typical foam cells in the bone marrow of the scapula. The chemical examination of the serum showed normal values of cholesterols, as well as phospholipids. The chemical determination of cholesterol in the biopsy tissue from the bone marrow exhibited increased figures for total cholesterol (2 mg. per cent) but these were not as high as those found in other tissues by Chiari and Epstein [30] (18.58 mg. per cent), Kleinmann [60] (15.8 mg. per cent) and Letterer [63] (9.6 mg. per cent); these were percentages of the dried tissue. In Case 1, 9 mg. per cent were found and in Case 9, 13.1 mg. per cent. Our Case 20 was unusual insofar as the bones only were involved by xanthomatous changes, but two similar cases have been reported by Fraser.[40]

The case of Letterer,[63] which also exhibited bone changes without diabetes insipidus and without skin manifestations, showed as an outstanding

feature a xanthomatous involvement of the lymph nodes as in Hodgkin's disease. There were no figures of the cholesterol content of the serum because the patient was diagnosed during life as having Hodgkin's disease,

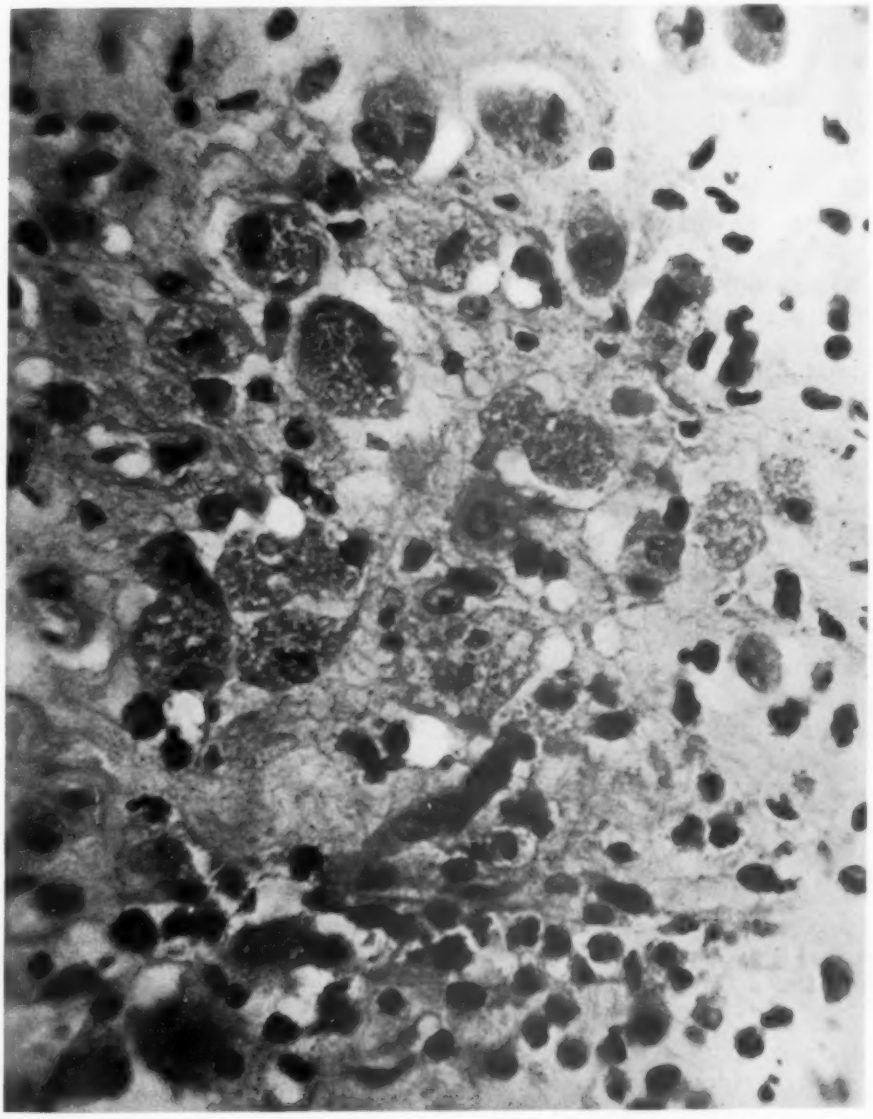


FIG. 37. Case 20. Histological picture of a xanthomatous nodule of the bone marrow.

although the serum was grossly reported as lipemic. The granulomatous features were so prominent that Letterer speaks of xanthomatous (in the original, xanthoeser) lymphogranulomatosis. Merrill (1920) [75] described a case of multiple bone lesions with xanthomata tuberosa and plana and

tendon xanthomata. The cholesterol content of the blood is reported as very high (figure not given). The published photographs showed the bone cysts to be of very small size and the evidence that they were true xanthomatous bone cysts not convincing. There is in the literature not one undoubted case reported of tendon xanthomata and xanthomata plana associated with xanthomata of the bones, whereas xanthomata disseminata are usually seen in such patients affected with osseous xanthomata. Further, normal serum cholesterol values are reported in such cases. Another doubtful case of xanthomatosis involving only the bones is reported by Snapper and Parisel.[124] Their patient, a girl, showed brown nevi on the skin but not xanthomata. The bone biopsy showed changes similar to those in osteitis fibrosa cystica. Another biopsy was reported to have shown foam cells. According to the paper of Allbright, Butler, Hampton and Smith,[1a] the case of Snapper and Parisel [124] does not belong to true osseous xanthomata. Two cases reported by Chester [28] as lipoid-granulomatosis, one a woman of 44, the other, a man of 69, were found to have extensive xanthomata of the bones. In neither of these cases was diabetes insipidus or exophthalmos observed during life. Xanthomatous involvement of the lungs and pleura was found at autopsy.

Our case 20 belongs to those unusual cases of xanthomata where the granulomatous features of the tissues were predominant, and xanthoma cells scarce. The low cholesterol values in the analyzed tissue are the chemical expression of this fact. However, there is no doubt that, according to the biopsy, Case 20 exhibited xanthomatous involvement of the bones.

The attempt has been made in the description of these 20 cases and in the discussion of the literature to distinguish between two clinical groups of primary xanthomatous diseases. The characteristic features in the one group are: (1) xanthomata plana and tuberosa; (2) tendon and tendon sheath xanthomata; (3) xanthomatous involvement of the wall of the bile duct with xanthomatous biliary cirrhosis; (4) xanthomatosis of the wall of the blood vessels and endocardium; (5) high values of total cholesterol in the serum, increased fraction of lecithin and cephalin; increased fat; (6) eruptive form of skin xanthomata; (7) xanthoma cell nests in the spleen, lymph nodes and liver.

The features of the other group are: (1) xanthomata disseminata of the skin, mouth and larynx; (2) xanthomatous involvement of the pituitary and tuber cinereum with the features of diabetes insipidus, xanthomata in the brain and medulla; (3) xanthomatous nodules on the dura and orbit; (4) osseous xanthomata; (5) xanthomatous involvement of the lung and pleura with consequent fibrosis; (6) normal or high normal total cholesterol in the serum, normal lecithin and cephalin fraction; normal fat; (7) scattered nests of xanthoma cells in the spleen, lymph nodes and liver (also present in the first group).

The two groups differ in the organs involved as well as in the lipid chem-

istry of the serum. The main histological findings in all types of lesions are the same, namely: xanthoma cells, granulomatous scar tissue with giant cells and exudate cells, varying according to the age of the lesion. We would like clinically to distinguish these two groups of xanthomatous diseases as "hypercholesteremic" and "normocholesteremic" types. We must, however, be aware that the underlying disease, that is "essential xanthomatosis," is the same in both groups.

Only three cases, where the organs involved by the xanthomatous process comprise both groups in one patient, could be found in the literature: (1) Hardaway (1889) [49]; (2) Weidman and Freeman (1924),[149] Griffith (1922) [46] (case is identical with Weidman and Freeman); (3) Weidman and Stokes (1937),[150] Gitting (1929) [45a] (case is identical with Weidman and Stokes). Hardaway's patient exhibited xanthomata disseminata (face, neck, axillae, trunk, extremities, as well as mucous membranes of the mouth and larynx), osseous xanthomata of the long bones, xanthomatous lesions in herpes zoster as well as hepatic cirrhosis with jaundice and xanthomata of the tendons. Hardaway speaks of a xanthomatous diathesis. He suggested, like Quinquaud, 1879,[95a] who used the expression "diathèse xanthomatique," that xanthoma formation is a "diathetic affection" and that its connection with hepatic disease was entirely secondary or, in other words, that jaundice occurring during the course of the disease was a consequence of "a deposition of xanthomatous tubercles in the liver."

Weidman and Freeman's patient [149] is the most completely studied case, illustrating the combined group; excellent histological photographs of all organs involved are published. This nine year old boy showed, as did Hardaway's patient, xanthomata disseminata and xanthomata plana, "hundreds of little nodules on mouth, neck, axillae, elbows, knees, also in the lines of the palms. The margins of all four lids have long flat lesions. There were several nodules on the side of the head, the underlying bones were depressed and roentgenograms showed small bony defects of the frontal and parietal regions." The boy was jaundiced, polyuric (diabetes insipidus) and had an enlarged liver. Total cholesterol 397 mg. per cent. The post mortem revealed xanthomatous involvement of the skin, brain, pituitary and tuber cinereum, diffuse xanthomatosis of the lung, xanthomatous biliary cirrhosis, xanthomatous changes in the lymph nodes, xanthomata of dura and skull.

The third case of the combined type, a girl 6 years of age, reported by Weidman and Stokes,[150] showed tuberous xanthomata in operative scars, and in our opinion the eruptive form of xanthomata, associated with a very high blood cholesterol (1039 mg. per cent). (Gitting [45a] reported in 1928 the same case with a blood cholesterol of 120 mg. per cent.) There was also diabetes insipidus but no exophthalmos. The roentgenogram did not show skull involvement. There were xanthomata on the roots of the teeth; jaundice and a large liver. No autopsy.

## Classification of Essential Xanthomatosis

At the present time, primary xanthomatosis is classified by Rowland [102] as embracing skin and mucous membrane, tendon sheath and visceral varieties; also as a separate entity—Schueller-Christian's disease. Buerger [25] classifies the disease into three groups: (1) essentially osseous, (2) essentially cutaneous and (3) essentially visceral localization. On study of our 20 cases and the reported cases in the literature, it seems to us that the clinical pictures and the anatomical facts do not warrant such a division. The clinical pictures show conclusively that the xanthomatous manifestations of the skin are different in appearance and significance. We tried to point out that certain well characterized forms of xanthomata of the skin are correlated with different xanthomatous manifestations of various organs. Two different groups of primary xanthomatosis are distinguishable without difficulty. Both groups differ, not only in the visceral organs affected and the skin manifestations, but also in chemical findings in the serum (hypercholesteremia on the one hand and normocholesteremia on the other). The description of three cases in the literature, where the features of both groups of xanthomata are found in one patient (combined group) reveals conclusively that primary xanthomatosis is a systemic disease. Primary xanthomatosis (metaplastic reticular cholesterosis) may occur isolated in one organ or combined in two different groups of organs or generalized in all organs which contain reticulum cells and histiocytes.

## Therapy of Essential Xanthomatosis

The two groups of xanthomatous diseases respond differently to therapeutic procedures. The xanthomatous diseases of the hypercholesteremic type show a marked decrease of the hypercholesteremia, as well as a decrease of the other blood lipids after a period of cholesterol and fat-poor diet. Such diets have been described by me.[137] They contain only vegetable fats because plant sterols are not absorbed (Schönheimer [115]). The xanthomatous diseases of the normocholesteremic type do not respond to diet treatment at all. We applied in both groups, in addition to the diet treatment, small doses of Thyroidin, one grain daily, with good effect in the hypercholesteremic group, while in the normocholesteremic group an influence on the cholesterol content of the serum was not evident.

The osseous xanthomata and the dura xanthomata of the cases of the normocholesteremic type respond to roentgen-ray therapy very satisfactorily according to Sossman and other authors. Whether the other organs (skin, lungs, brain) belonging to the symptom complex of the normocholesteremic type react to roentgen-ray favorably is not known. The skin xanthomata belonging to the group of the hypercholesteremic type, however, as well as the tendon xanthomata, are not influenced at all by roentgen-ray.

## Secondary Xanthomatosis

The two cases to be reported here were observed at the Deaconess Hospital by Dr. Elliott P. Joslin and his associates, to whom I am indebted for the privilege of publishing the records.

*Case 21.* The patient was in acidosis when first seen by Dr. Joslin, January 15, 1934. Glycosuria 7.4 per cent; blood sugar 250 mg. per cent; insulin 56 units daily. He showed lipemia retinalis and an eruption characterized by nodular pustules, surrounded by narrow pink zones.

The localization of these nodular-pustular eruptions which come and go is usually all over the body except for the scalp. The nodular pustules vary in size from a small pinhead to a grain of wheat. There are a few larger lesions formed by the confluence of adjacent lesions. The lesions for the most part consist of a light yellow tip upon an inflammatory reddish base, which may change color in due course to violet and brown. Except on close inspection, they would be taken for true pustules. Indeed, physicians and patients have opened them in an effort to remove the yellow material seemingly present on the tip and have been puzzled to get only blood and a little white serum. It is noticeable that the lesions do not always have a yellow tip; therefore the etiology is usually not recognized. Some of the lesions are excoriated by scratching, due to itching. These lesions come and go. In this case, they had disappeared within five months after insulin and diet treatment was instituted which had effected also a complete disappearance of the lipemia.

| Date | Cholesterol | Blood Sugar |
|---|---|---|
| 1/15/34 | 1600 | 0.21 |
| 1/16/34 | 1520 | 0.21 |
| 1/17/34 | 1344 | |
| 1/18/34 | 1376 | 0.21 |
| 1/19/34 | 1248 | 0.21 |
| 1/20/34 | 1248 | 0.27 |
| 1/22/34 | 1184 | 0.27 |
| 1/27/34 | 792 | 0.19 |
| 2/3/34 | 416 | 0.15 |
| 2/17/34 | 294 | 0.18 |
| 3/15/34 | 175 | 0 19 |
| 5/3/34 | 172 | 0.26 |
| 6/9/34 | 205 | 0.16 |

*Case 22.* Patient 32 years of age, seen September 18, 1934. Weight 132 pounds. Insulin 52 units. Feels fine. Diabetes discovered in December 1925. The diagnostic remark was "a mild diabetes, but not very coöperative." Eight years later the patient was seen again. At this time, April 29, 1933, hard xanthomatous lumps were found in the right heel. Plasma cholesterol was 644 mg. per cent; blood sugar 120 mg. per cent. On August 17, 1934, simultaneously with lipemia and definite lipemia retinalis, an eruption appeared of many small yellowish papules scattered diffusely on arms, chest and lower back. Glycosuria 3.3 per cent. Blood sugar 220 milligrams. Plasma cholesterol 768 milligrams.

*Comment and Discussion.* We owe the first description of this kind of eruptive xanthomata to Addison and Gull,[1] who described its occurrence in a diabetic in the historical paper already mentioned as giving the first description of xanthomata plana and tuberosa with biliary cirrhosis. Their description follows:

"The eruption somewhat suddenly appeared on the arms. . . . In the course of

ten days, it had extended over the arms, legs and trunk, both anteriorly and posteriorly, also over the face and into the hair; it consisted of scattered tubercles of various sizes, some being as large as a small pea together with shining, colorless papules. They were most numerous on the outside and back of the forearm, and especially about the elbows and knees, where they were confluent. Along the inner side of the arms and thighs, they were more sparingly present, and entirely absent from the flexures of the larger joints. Besides the compound character produced by the confluence of two or three tubercles, which appeared to be such, as shown by the prominent whitish nodules upon them, some looked as if they were beginning to suppurate, and many were not unlike the ordinary molluscum, but when incised with a lancet, they were found to consist of firm tissue, which on pressure gave out no fluid save blood.

"They were of a yellowish color, mottled with a deepish rose tint, and with small capillary veins here and there ramifying over them. They were accompanied with a moderate degree of irritation, hence the apices of many were rubbed and inflamed. . . ."

This eruptive form so excellently described almost ninety years ago was characterized as "xanthoma diabeticorum." Many authors designate as xanthoma diabeticorum not only the eruptive form, which comes and disappears simultaneously with the lipemia, but also xanthomata tuberosa and plana, which are persistent. This confusion results from the fact that xanthomata tuberosa and plana are observed simultaneously with a mild diabetes as described in our Case 22 and in Case 4. In these cases, xanthomata tuberosa are features of primary xanthomatosis, when at the same time as the skin, visceral organs are involved. Xanthomata diabeticorum on the contrary are not the cause but the sequel of a complication in diabetes. This complication is lipemia. Xanthomatosis diabeticorum, that is the eruptive form of xanthomata, occurs not only in high lipemia during severe diabetes, but also in primary xanthomatosis, if high lipemia is present. This fact is evident in the three cases with xanthomatous biliary cirrhosis without diabetes but with lipemia. The eruptive form of xanthomata described and pictured in these cases of primary xanthomata is identical in appearance as well as in its transitory character with the eruptive form of xanthomata occurring in severe diabetes without primary xanthomatosis, and known as xanthomata diabeticorum. In the above described Case 22, tuberous xanthomata and mild diabetes were present for many years until rather suddenly lipemia was noted as lipemia retinalis and the eruptive form of xanthomata occurred. The eruptive form of xanthomata and lipemia disappeared, but the xanthomata tuberosa and hypercholesteremia persisted. A similar case is described by Major [71, 72] (1924), who pointed out that xanthomata diabeticorum is connected with lipemia and not primarily with diabetes.

We should like to emphasize that the eruptive form of xanthomata (xanthoma diabeticorum) is etiologically entirely different from all xanthomata due to primary xanthomatosis. The latter is a systemic disease. The eruptive form is a symptom of lipemia and may occur in diabetic

lipemia as well as in lipemia during xanthomatous disease as in xanthomatous biliary disease.

We have already pictured the histological findings of the eruptive form of xanthomata (figure 22). In the photographed specimen xanthomata cells are not found. But there are reports in the literature that besides the signs of inflammation, there are found some rare xanthoma cells. R. H. Major points out this difference from true xanthomata. He described his findings as follows:

"A section from one of the excised nodules showed marked evidence of inflammation. The corium was thickened, extensive keratinization had taken place; there were areas of small, round-cell infiltration; marked fibrotic changes present and the characteristic large xanthoma cells were recognized with difficulty."

The xanthomatous lesions described by Urbach [142] as extracellular cholesterosis should now be discussed. "The essential lesions are lentil-sized, hard translucent nodules, sometimes with a central blister. After one or two days they become blue-violet, generally with a yellow center and later still reddish-brown. . . . Sometimes at the beginning the eruptions resembled erythema multiforme. . . . Some of the lesions disappeared after a few days and even nodes of long duration regressed considerably under roentgen-ray." The histological findings in Urbach's nodules of extracellular cholesterosis exhibit vascularity of the cutis with damage to the vascular endothelium and infiltration with round and spindle cells. In none of the preparations was there the slightest indication of foam-cell formation. The lipoid was entirely extracellular, first around the vessels and later in the whole cutis. The lipid was found by staining and chemical analysis of the lesion, which revealed a cholesterol to cholesterol ester ratio of 3:1 in contrast with true xanthomata tissue of 1:1.5. These figures are impressive indeed. But if we really considered the material chemically analyzed in the case of the eruptive xanthomata (extracellular cholesterosis), the value of those figures is doubtful because the quantity of material must have been minimal and the quality of material is varying and uncontrollable in view of the minimal amount of pathological tissue and the amount of healthy tissue chemically examined in the same specimen. Chemical analysis of pathological tissue is of value only if a large amount of characteristic tissue like true xanthomata can be analyzed. Be the value of the chemical findings what it may, the clinical description of the lesions of "extracellular cholesterosis" by Urbach is in conformity entirely with the clinical appearance of eruptive xanthomata first described as xanthomata diabeticorum by Addison and Gull, and many subsequent authors.

The differential diagnosis of the eruptive form of xanthomata from xanthomata disseminata which are true xanthomata, that is, the skin manifestations of a systemic disease which simultaneously involves a group of organs, should not be difficult. The eruptive form is scattered, never in ridges, never mulberry-like or in warty clusters, nor are they pedunculated.

The lesions are isolated or in small groups. The color of the lesions in xanthomata disseminata is lemon yellow or in older lesions a deep reddish brown, mahogany-like. They grow in ridges and clusters with localization around the neck, axillae, and in the bend of elbows and knees.

Sometimes it may be difficult at first to differentiate the eruptions from erythema multiforme, but the colorations and vascularization of the nodule is characteristic after a few days so that the eruptive form of xanthomata cannot be easily mistaken. The blood findings of high cholesterols (the ratio of cholesterol to cholesterol esters may be normal in diabetes, and reversed in xanthomatous biliary cirrhosis), high fats and lipemia confirm conclusively the diagnosis already made clinically.

That the eruptive forms of xanthomata and xanthomata diabeticorum are identical should be emphasized. Hyperlipemia and hypercholesteremia result in this kind of skin eruption, which we consider as secondary to the high grade of lipemia occurring in the course of severe diabetes mellitus or in the course of xanthomatous biliary cirrhosis. Therefore, the skin manifestations of primary xanthomatosis must be differentiated from the eruptive form of xanthomata, the so-called xanthomata diabeticorum, which are classed in the group of secondary xanthomata. Xanthomata tuberosa, on the other hand, are independent features of primary xanthomatosis and occur at times with diabetes mellitus. Their presence in diabetes is an indication that the systemic primary xanthomatous disease involves also visceral organs, possibly the pancreas.

Severe lipemia, during diabetes mellitus, produces, not only in the skin but also in other organs, changes which are histologically very similar to those of xanthomatous disease. This kind of xanthomatous change occurring in the spleen and lymph nodes belongs also to the group of secondary xanthomata because the lipemia is the primary occurrence and the xanthoma cell formation is due to a secondary deposit in reticular cells and histiocytes. W. H. Schultze[121] (1912) described first "large cell hyperplasia of the spleen during lipemia" and shows that little nests of xanthoma cells occur in the spleen as a result of lipemia in diabetes mellitus. Lutz,[67] Williams and Dresbach,[158] Pick,[84] Margaret Smith,[123] W. Schöndorff,[109] S. Warren and Root[147] describe such large cell hyperplasia in diabetes with lipemia. We are inclined to classify the case which Lubarsch[66] described in 1918 under the title "Generalized Xanthomata and Diabetes" as the most outstanding example of this group of secondary xanthomatosis. This patient suffered and died of severe diabetes with lipemia. The liver, spleen, kidneys and especially lymph nodes and the walls of the lymph vessels exhibited large patches of xanthoma cells (lymphangitis xanthomatosis). There was no xanthomatosis of the skin but xanthosis of the skin was found. Xanthosis of the skin is almost always associated with the first group of primary xanthomatous diseases of the hypercholesteremic type (Cases 4, 6, 9, 11), but xanthosis of the skin has nothing to do with xanthoma formation.

Xanthosis, first described by von Noorden [81] in diabetes mellitus, is a symptom which may occur without diabetes in all conditions of lipemia and even without lipemia if carotine is increased in the serum. The significance of the coincidence of hypercholesteremia and hypercarotinemia is unknown. Xanthoma cell formation in the reticular apparatus was a secondary process due to lipemia similar to the more localized forms described in the spleen and in lymph glands. Certainly we cannot prove that Lubarsch's case belongs to this group of secondary xanthoma cell formation. However, the complete absence of skin xanthomata of both groups (xanthomata tuberosa and plana on the one hand and xanthomata disseminata on the other hand) while xanthosis was present, in addition to the clinical course of the disease is highly in favor of this assumption. We have already suggested above that Buerger and Grütz' cases of hepatosplenomegaly without jaundice but with extreme lipemia may belong to this group of secondary xanthomatosis resulting from lipemia. The lipemia in these cases is of unknown origin. Chronic cirrhosis of the pancreas may result in such extreme lipemia, but in contrast to the lipemia in diabetes mellitus, this lipemia condition is scarcely influenced by diets poor in fats. Attempts already made by different authors (Anitschkow,[3, 4, 5] Kawamura [57] and McMeans [70]) to reproduce xanthomatosis by the feeding of cholesterol, or to reproduce Gaucher's disease by intravenous injection of cerebrosides (Kimmelstiel and Laas [59]) and Niemann-Pick's disease by injection of phosphatides (H. Bäumer and G. B. Gruber) [14] lead to similar histological pictures in the spleen and lymph nodes as described by Schultze and others, as "large cell hyperplasia of the spleen during lipemia." It is evident that the reticular cells and the histiocytes are able to take up out of the blood, cholesterol as well as cerebrosides and diaminophosphatides. In so doing, these cells change in appearance and assume the shape of foam cells. This procedure of injection of lipids, however, does not reproduce either the clinical syndrome or the complex anatomical picture of any of these "lipoid diseases," but it does reproduce histologically similar organic changes in the spleen, lymph nodes, and in extreme cases also in the liver (described by Schultze [121] and others) to those that occur in association with lipemia in diabetes mellitus. It may well be that the mechanism of xanthoma cell formation in essential xanthomatosis is entirely different from the procedure which only attempts to increase the lipids in the blood by feeding or intravenous injection.

## The Etiology of Xanthoma Formation

The different clinical symptoms of essential xanthomatosis having been presented, the etiology of xanthoma formation in this systemic disease will now be discussed.

Waldeyer (1871)[146] considered the cells of xanthomata plana, afterwards called foam cells, to be embryonal cells which had the possibility of forming different kinds of fats and of releasing the fat by degeneration.

Virchow [145] described under the heading "xanthoma multiplex mulluscum lipomatoides," xanthomata disseminata of the skin as little benign neoplasms. Following the opinion of Virchow, xanthomata in general were considered in the literature to be "benign tumors." "*Ce sont donc les cellules endotheliales des espaces lymphatiques qui par leur proliferation, forment la tumeur xanthomateuse*" (classified as "endotheliome adipeux" by de Vincentis [143]). Pönsgen,[89, 90] Koebner [61] accept the opinion of Waldeyer,[146] that cells which remained in an embryonal stage produced by their proliferation and adipose metamorphosis a so-called "embryonal lipoma" which is identical with the xanthomata. Török [138] says that it is better not to classify xanthomata as true tumors but as abnormality of formation "*il* (*xanthoma*) *se forme du tissue a une endroit hétérotopique et il est constitué en raison même de cette heterotopie par des cellules adipeuses a évolution interrompue incomplète*" (*embryonale*).

Pinkus and Pick (1908) [87, 88] found the fat substances in the xanthoma lesions to be doubly refractile lipids, cholesterol and cholesterol esters. These authors suggested that hypercholesteremia may be the genesis of xanthomatosis. "Cholesterol infiltration of certain cells takes place because of an increased cholesterol supply from the blood." This hypothesis was advanced after Aschoff [8, 9] and his pupils had demonstrated that reticulo-endothelial cells were able to take up from the blood different kinds of dyes, as well as fat-like substances. Anitschkow [3, 4, 5] in Aschoff's Institute found that by feeding rabbits cholesterol, foam-cells could be produced. On the other hand he was able to demonstrate that the same cells which changed to foam-cells also took up substances foreign to the body such as dyes. Indeed, these cells which have the characteristic of storing doubly refractile substances, as well as dyes, belong to those cells which Aschoff [9] classifies as the reticulo-endothelial system. Because hypercholesteremia was believed to be essential for xanthoma cell formation it was natural to assume that the surplus of cholesterol in the serum due to a general disturbance of the cholesterol metabolism is taken up and stored by the reticulum cells, and results in a pathological change of the tissue forming xanthomata. This hypothesis is widely accepted in the literature. The proof, however, that there exists such a disease as a general metabolic disturbance of the cholesterol metabolism, which is the prerequisite of this assumption, is lacking. Appreciating this weak point of this hypothesis, Bloch [18] and Schaaf [103] explain that cholesterol represents only one element in a very complex mixture of fat and lipids in the serum. "This mixture of lipid constituents does not exist in the serum in a dissolved form, but in the form of a finely dispersed emulsion. The normal proportion of all the lipid constituents must be maintained in the blood. If the proportion is changed in any direction, i.e. if the proportion of cholesterol to lecithin or to cerebrosides or sphingomyelins is altered, the result according to the laws of the colloid theory is a disturbance in the stable aqueous lipid emulsion which the serum represents.

The particles become coarser, the emulsion separates, and finally there is a precipitation of one or all of the individual constituents in the blood and tissues and a deposit of material, so that xanthomatosis results." This hypothesis of Bloch [18] and Schaaf [103] has also as a prerequisite an extracellular general metabolic disturbance of the lipids, which results secondarily in a deposit of lipids in the reticular cells and the tissue. There is neither proof of a colloid decomposition of the serum or cell fluids resulting in precipitation nor any evidence that a disproportion of the lipids in the serum or tissue may lead to a flocculation of the colloid mixture. Deposits of lipids, especially cholesterol, are found in deteriorated tissue and in places where cells containing cholesterol undergo destruction. Up to the present we do not know of a spontaneous decomposition of a colloidal system of lipids in the serum even when the constituents of this system are markedly changed in their relation to each other. The colloid systems protected by different mechanisms in the organism are not to be compared with colloid systems prepared in the test tube because it is only partially and inadequately possible to copy the constituents of the colloid mixture in the body. The hypothesis of Bloch and Schaaf which adds to the assumption of extracellular disturbance of the lipid metabolism, a second hypothesis which has not been proved at all, does not stand critical analysis from the chemical point of view.

There remains to discuss as the main question, whether essential xanthomatosis is due to a general metabolic disturbance of cholesterol metabolism, which leads to an increased cholesterol supply to the reticular cells and a consequent storage of cholesterols and lipids in these cells (cholesterol infiltration of L. Pick [85, 88]), or whether the metabolic disturbance is an intracellular metabolic disturbance confined to the reticular cells themselves, which may become xanthoma cells not by an increased supply but as the result of an intracellular metabolic disorder. The problem is, therefore, whether essential xanthomatosis is due to a disturbance of the intermediary cholesterol metabolism or whether it is caused by an intracellular metabolic disorder limited to certain reticular cells. Considering the mechanism of an intermediary disorder of the cholesterol metabolism, four possible processes of cholesterol metabolism may play a part.

(1) There may be a diminished disintegration of cholesterol in the intermediary metabolism. The xanthomata would then be the expression only of its retention and storage.

(2) There may be a diminished excretion and output of cholesterol and coprosterol in the feces. In such a case the xanthomata would be, as in the first process suggested, the result of retention and storage of cholesterol.

(3) The equilibrium between cholesterol and cholesterol esters may be disturbed so that sufficient cholesterol esters are not formed to transport an adequate amount of cholesterol. For the same reason the other lipids,

especially the phospholipids, may be involved and a disturbance of the lipid mixture may result.

(4) There may be an increased synthesis of sterols. This increased synthesis may occur in organisms as a whole, and the sterols ubiquitously synthesized in the body are taken up out of the blood by reticular cells and stored. Or the increased cholesterol formation is performed by certain reticular cells which are able to synthesize and release cholesterol, but in the process as the result of an intracellular imbalance reticular cells assume the appearance of xanthoma cells. On the basis of the physiology of the intermediary cholesterol metabolism, which we have discussed earlier, we believe we are able to answer these four questions as to whether or not essential xanthomatosis is the result of a disturbance of the intermediary cholesterol metabolism.

The first assumption suggests a diminished disintegration of sterols in the intermediary metabolism. We have shown in our physiological discussion that there is no disintegration of cholesterol in the intermediary metabolism. Neither bile acids nor other sterols occurring in larger quantities in the organism are derivatives of cholesterol disintegration. The human organism is able to synthesize the sterol skeleton but cannot disintegrate it by means of fermentative processes.

In the second suggestion the question was raised whether a decrease of the cholesterol excretion could explain the essential xanthomatosis. Such an assumption should be easily answered by determining the cholesterol balance, but unfortunately the determination of cholesterol excretion in the feces cannot decide conclusively the cholesterol balance, because an uncontrollable amount of cholesterol may be destroyed by bacteria of the feces (according to Bertha Ottenstein). On the other hand, we have demonstrated that a diet free of animal sterols decreases the cholesterol content of the blood in cases of tendon xanthomata as well as in xanthomatous biliary cirrhosis. On the basis of an experiment carried out on a patient with tendon xanthomata where the total cholesterol dropped from about 800 mg. per cent to almost normal values, Schönheimer and I have been inclined to believe that retention of sterols plays an important part in formation of xanthomata. The opinion was expressed that these patients behave like herbivorous animals, which can absorb but not excrete cholesterol. However, we had to change our minds because several of our patients (Cases 1 and 9) on a cholesterol-free diet showed insufficient reduction of the cholesterol in the serum, and we found that xanthomata tuberosa as well as tendon xanthomata were not altered even when the blood cholesterol had returned to almost normal values. The most important argument against the assumption that a disturbance of cholesterol output is the main cause of essential xanthomatosis is the fact that in the group of xanthomatous diseases characterized by xanthomata disseminata of the skin, involvement of the brain (diabetes insipidus), involvement of the bones, lungs and lymph

nodes, the cholesterol values in the serum were normal or high normal. Even in the other group, the hypercholesteremic type, which comprises xanthomata tuberosa and plana, tendon xanthomata, xanthomatous biliary cirrhosis, etc., we were able to find almost normal cholesterol figures (Cases 2 and 11) with beginning tendon xanthomata. A diminished output may play some rôle in the clinical course of essential xanthomatosis, but it is evident that this is not the main cause of this systemic disease.

The third possibility was a disturbance in cholesterol-ester formation or of a disproportion of cholesterols to phospholipids. In the literature and in our cases, the increase of total cholesterol, where there is an increase, is due to an increase of esters. The only exception to this finding of normal or high cholesterol esters in xanthomatosis was in patients with xanthomatous biliary cirrhosis where we found an inversed ratio of cholesterol to cholesterol esters in the serum. This is due to the liver damage and not to the xanthomatous disease (Thannhauser and Schaber [131]). The normal or high cholesterol esters in the blood and the high content of cholesterol esters in xanthomatous tissue show conclusively that there is no disturbance of ester formation which could cause difficulties in cholesterol transportation and lead to an abnormal deposit of cholesterol. Only in old granulomatous scar tissue of xanthomata, as in tendon xanthomata, free cholesterol prevails over ester-cholesterol, and sometimes crystallizes in the tissue. This tissue may have partially softened into a yellowish detritus. In the scars of these xanthomata foam cells are still scarcely found having been replaced by granulomatous tissue or softened to a yellowish, semi-fluid mass. Cholesterol esters are absorbed easier from such broken down foam cells while free cholesterol remains and crystallizes " in loco." (Figure 4, Case 1.)

The figures for fat, cholesterol, cholesterol esters, monoaminophosphatides (lecithin and kephalin) and diaminophosphatides (sphingomyelins) of our series of cases are summarized here. These findings demonstrate that in xanthoma diseases of the hypercholesterol type, an increase of total cholesterol is usually accompanied by an increase in fat and monoaminophosphatides (lecithin and kephalin), while in the group of xanthomatous diseases of the normocholesteremic type, fat and monoaminophosphatides are also normal. We would like to infer from these figures that xanthomata formation is *not* caused by a disproportion of the lipid mixture in the serum, because in the group of xanthomata without an increase of cholesterol, the fat and monoaminophosphatides are normal, and in the group of xanthomata with high cholesterol, fat and monoaminophosphatide are increased proportional to the sterols.

The fourth suggestion deals with the question as to whether an increased cholesterol synthesis carried out everywhere in the organism and followed by a consequent storage of cholesterol in the reticular cells is the cause of essential xanthomatosis. Such an increased cholesterol synthesis as an expression of a general metabolic disturbance should lead in all clinical

| | Total cholesterol mg. % | Free cholesterol mg. % | Cholesterol esters mg. % | Total P. Lipid mg. % | Diaminophosphatide (sphingomyelin) mg. % | Monoaminophosphatide (lecithin and cephalin) mg. % | Total fat as fatty acids mg. % |
|---|---|---|---|---|---|---|---|
| Normal | 110–220 | 40–80 | 70–140 | 200–350 | 100–150 | 100–150 | 200–400 |
| *Essential Xanthomatosis of the Hypercholesteremic Type* | | | | | | | |
| Case No. | | | | | | | |
| 1 | 308 | 240 | 128 | 375 | 265 | 110 | |
| 2 | 210 | 107 | 103 | 330 | 180 | 150 | |
| 4 | 476 | 125 | 351 | 437 | 243 | 194 | 1088 |
| 5 | 276 | 75 | 201 | 290 | 81 | 209 | 527 |
| 6 | 216 | 50 | 166 | 309 | 112 | 197 | |
| 7 | 265 | 107 | 158 | 450 | 150 | 300 | 577 |
| 8 | 533 | 129 | 404 | 394 | 132 | 262 | 585 |
| 9 | 667 | 203 | 464 | 448 | 194 | 254 | 484 |
| 11 | 282 | 97 | 185 | 303 | 137 | 166 | 471 |
| 12 | 400 | 100 | 300 | | | | 471 |
| 13 | 500 | 183 | 317 | 632 | 83 | 549 | |
| *Essential Xanthomatosis of the Normocholesteremic Type* | | | | | | | |
| 18 | 208 | 74 | 134 | 260 | | | 290 |
| 19 | 195 | 67 | 128 | 650 | 84 | 566 | 276 |
| 20 | 150 | 40 | 110 | 278 | 117 | 161 | |
| 23 | 191 | 52 | 139 | 228 | 30 | 198 | 320 |

syndromes of essential xanthomatosis to hypercholesteremia. Hypercholesteremia is, however, found only in one group of xanthomatous organ involvement, while the other group shows a normal amount of cholesterol, in spite of the fact that the same histological constituents are found in both groups. This is definitely against the assumption that xanthomata result from a general metabolic disturbance of cholesterol synthesis and favors the idea that we have to deal with a local cellular metabolic disturbance which may involve one organ only in a small area or groups of organs far apart.

In considering the four possible general disturbances of intermediary cholesterol metabolism discussed above, the following statements can be made. There is no definite proof to justify the assumption that primary essential xanthomatosis is caused by a disorder of the intermediary cholesterol metabolism. The generally accepted theory of L. Pick [86, 87, 88] which suggests a general disturbance of the cholesterol metabolism followed by a secondary deposit of cholesterol in the reticular cells as the cause of essential xanthomatosis is untenable, since the experiments concerning the normal metabolism of cholesterols do not give the slightest evidence of an inter-

mediary disturbance of cholesterol metabolism. We would rather believe that the metabolic disturbance of the cholesterol is localized in those cells themselves which are called xanthoma cells after their content. Besides the reasons already mentioned, the experiments of Biedermann and Hoefer [17] speak in favor of our suggestion of a localized cellular metabolic disturbance. These authors used tissue cultures of tissue prepared from xanthomatous nodules. They were able to demonstrate that the xanthoma cells of the cultivated tissue increased and emigrated. Some of the cells which had grown were identified as xanthoma cells by their content of doubly refractile substance.

It is evident from these experiments that the xanthoma cells themselves form the doubly refractile substance and a further proof for the genesis of xanthoma cells by an intra-cellular metabolic disturbance is added by the analogy which primary essential xanthomatosis bears to the other diseases of lipid metabolism, namely: Gaucher's and Niemann-Pick's disease. In all three of these diseases large cells with fatty content arise in different organs. In essential xanthomatosis these cells contain cholesterol and other lipids. In Gaucher's disease these cells contain cerebrosides, while in the Niemann-Pick's disease the content of these cells consists of diaminophosphatides (sphingomyelins). According to the suggestion of L. Pick, it was generally assumed that these three diseases were caused by the storage (infiltration) in the reticular cells of these lipids produced in excess by the intermediary metabolism of the organism. Concerning Niemann-Pick's disease, Baumann [18] has already demonstrated that the content of total phospholipids (mono- and diaminophospholipids) is normal and even lower than normal in the blood. The sphingomyelins, however, are found in abnormal quantities only in the Niemann-Pick cells. In Gaucher's disease, Thannhauser, Reichel, Dameshek and Walcott [unpublished] were able to prove in four cases, that only traces of cerebrosides were present in the serum of these patients, as is the case in normal serum. These investigations show that at least for Gaucher's disease, but probably also for Niemann-Pick's disease, the lipid substances involved in the particular disease are not formed in the intermediary metabolism and secondarily deposited in the reticular cells, but are formed and stored in the cells themselves. Gaucher's and Niemann-Pick's disease may, therefore, be considered as due to an imbalance of intra-cellular ferments (Thannhauser and Reichel [136]). We believe essential xanthomatosis, which belongs to the same group of lipid diseases, to be analogous to the above two diseases in that it is caused by an intracellular metabolic disturbance of certain reticular cells. In these cells cholesterol especially, but also other lipids, are found to be increased and stored, so that the xanthoma cells result.

In assuming a cellular disturbance to be the etiology of primary essential xanthomatosis, we return to the view of former investigators, Waldeyer,[146] de Vincentis,[143] Hallopeau [46a] and Török.[138] According to these authors

the xanthoma cells are fat cells with embryonal qualities. With present day interpretations, we would say that these embryonal reticular cells, as far as their metabolism is concerned, are able to form *all* kinds of lipids. At that time the knowledge of metabolism was not sufficiently advanced to recognize the disorder which produced the xanthoma cell, as a cellular metabolic disturbance. The former assumption that the disorder is due to an embryonal metaplasia of certain cell groups is, however, identical with the idea that a cellular disorder is the cause of the disease " essential xanthomatosis."

To clarify further our interpretations of the mechanism of these cellular diseases, we may speak of essential xanthomatosis as " metaplastic reticular cholesterosis," of Gaucher's disease as " metaplastic reticular cerebrosidosis," and of Niemann-Pick's disease as " metaplastic reticular sphingomyelinosis."

The groups of secondary xanthomatous diseases are to be distinguished in principle from primary essential xanthomatosis (metaplastic reticular cholesterosis). In contrast to the primary essential xanthomatosis, which is a systemic disease resulting from an intracellular metabolic disturbance, the secondary xanthomatosis (eruptive form of xanthomata, formation of nests of xanthoma cells in the spleen, lymph glands and liver, large cell hyperplasia of Schultze) is a disease which is due to a storage of lipids which the reticular cells take up from the blood. An increase of cholesterol and other lipids in the serum as in lipemia during diabetes mellitus or as in lipemia of other origin, is the prerequisite of secondary xanthomatosis.

By suggesting that the formation of true xanthoma cells is due to an intracellular metabolic disorder of the reticular cells, we may explain the fact that xanthoma cell formation may occur independently of " essential xanthomatosis," as it does in localized tumors which have nothing in common with the systemic disease " essential xanthomatosis." Indeed, xanthoma cells are observed in different kinds of local tumors, such as fibrosarcoxanthomata, nevoxanthoendothelioma (Montgomery and Osterberg), etc.

As a result of the above study, and in order to clarify interrelationships between the type of xanthomata of the skin, and the various clinical patterns associated with each type, the following classification of xanthomatous diseases is offered.

## Classification

I. *Primary essential xanthomatosis* (metaplastic reticular cholesterosis).
   *A.* Primary essential xanthomatosis of the hypercholesteremic type.
      1. Xanthomata of tendons and tendon sheaths.*
      2. Xanthomata tuberosa and plana.
         2a. Forme fruste.
      3. Xanthomatous biliary cirrhosis resulting from xanthomatosis of the bile ducts.

* The recent papers of van Bogaert and Epstein describe the combination of tendon xanthomata with xanthomatosis of the central nervous system. We are inclined to classify this new syndrome under the group of tendon xanthomata until more cases of this type have been analyzed.

4. Xanthomatosis of the endocardium and blood vessels.
5. Eruptive form (if excessive lipemia is present) of skin xanthomata.
6. Scattered nests of xanthoma cells in the spleen, liver and lymph glands (these may also be present in group B).

*B. Primary essential xanthomatosis of the normocholesteremic type.*

1. Xanthomata disseminata of the skin (localized all over the body, neck, axilla, bend of knees and elbows, groins, mouth and larynx.)
2. Osseous xanthomata of the skull, scapula, pelvis, extremities and orbit.
3. Xanthomatous involvement of pituitary and tuber cinereum with features of diabetes insipidus. Xanthomata of brain, medulla and dura.
4. Xanthomatous involvement of the lung and pleura with consequent pulmonary fibrosis.
5. Scattered nests of xanthoma cells in the spleen, lymph glands and liver (these may also be present in group A).

*C. Primary essential xanthomatosis of the combined type.* (Cases of Hardaway, Weideman and Freeman, Weideman and Stokes.)

II. *Secondary xanthomatosis due to lipemia.*

1. Eruptive form of xanthomata. Xanthomata diabeticorum.
2. Nests of xanthoma cells in the spleen, lymph glands and liver with and without hepatosplenomegaly (Schultze's large cell hyperplasia in the spleen during lipemia).
3. Xanthomatous lymphangitis (Lubarsch).

III. *Localized xanthoma cell formation in true tumors.* (Nevoxantho-endothelioma, fibrosarcoxanthoma, etc.)

## Summary

1. The physiology of the cholesterol metabolism and its interrelationships with xanthomatous diseases is discussed.

2. A critical review of the literature is presented.

3. Twenty-two cases illustrating the different features of xanthomatous disease are described.

4. On the basis of the above study, three different symptom-complexes of primary essential xanthomatosis are presented and differentiated and a classification offered. Secondary xanthomatosis due to lipemia is distinguished from primary essential xanthomatosis.

5. Xanthomatous biliary cirrhosis and its relation to xanthomatous bile duct disease is described.

6. The eruptive form of xanthomata (xanthomata diabeticorum) is shown to occur not only in hypercholesteremia in diabetes mellitus, but also in xanthomatous biliary cirrhosis, xanthomata tuberosa and tendon sheath xanthomata if excessive hypercholesteremia is present.

7. Xanthomata disseminata has been shown to be characteristic only of the second (normocholesteremic) group.

8. It is shown that the general assumption that essential xanthomatosis is a storage disease of the reticular cells due to a disturbance of the general intermediary metabolism of cholesterol, is not in conformity with the physiological and clinical findings. Our studies suggest that essential xanthomatosis is a cellular disease of reticulum cells caused by an intracellular disorder of their cholesterol metabolism.

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# CASE REPORTS

## TORULA MENINGO-ENCEPHALITIS; A CASE REPORT *

By J. Homer Cudmore, M.D., F.A.C.P., and James R. Lisa, M.D., F.A.C.P.,
*New York, N. Y.*

Since the contribution of Freeman [1] on torula infection of the central nervous system, increasing attention has been paid to this interesting condition. Recently Levine [2] has again reviewed the literature, adding 17 more cases, including two of his own, bringing the total number to 60. The present case is reported, not so much because of the rarity of the condition, but to add a new and as yet unreported manifestation of the infection, a cicatrizing lesion of the brain.

### Case Report

The patient, a white male 30 years old, was admitted to City Hospital on March 15, 1935, complaining of severe headache and abdominal pain.

*Past History.* At the age of two years, he had scarlet fever. At 12, an enlarged cervical gland was diagnosed as tuberculous and treated by injection, possibly with an iodized oil. A biopsy, however, was not performed. At 14 and 16 there occurred attacks of pneumonia. From 26 to 28, he had severe epileptiform seizures which had continued in increasing frequency since then. He was drinking heavily when the seizures first appeared and they were attributed to this fact.

*Present Illness.* One week before hospitalization, he began to have excruciating headache, the pain radiating from the eyes to the temporal regions. After three days, it was associated with vomiting. Both symptoms increased in severity to the time of admission. There were no other pertinent data.

*Physical Examination.* He was a well developed and well nourished young man, extremely restless because of the headache. Mentally he was clear and coöperative. There was general hyperreflexia. Muscular, sensory and equilibratory tests were all normal. Abdominal reflexes were present. Pathological reflexes were absent. The pupils were equal, regular and reacted normally to light and accommodation. There were no ocular palsies. The fundi were normal. Except for a slight tachycardia, the other systems were entirely negative. The temperature was 99° F; pulse 60; respirations 20; blood pressure 110 mm. systolic and 70 diastolic.

The blood count revealed a leukocytosis of 10,400 with 62 per cent polymorphonuclears and 38 per cent lymphocytes. The Wassermann reactions on blood and spinal fluid, colloid gold curve and urine were negative. Chemical examination of the spinal fluid showed sugar 72 mg. per cent and chlorides 650 mg. Roentgenography revealed clouding of the right ethmoid sinus, marked sclerosis of the antral cells of the right mastoid and moderate sclerosis of the left antral cells, increased convolutional markings of the skull, and a greatly flattened sella turcica. The clinoid processes were not visualized. The pineal body was calcified.

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From the First Medical Service and the Pathological Laboratory, City Hospital, Welfare Island, Dept. Hospitals, New York, N. Y.

*Course.* The course was characterized by marked variability of the neurological symptoms. Periods of mental clarity alternated with drowsiness, severe headaches and nuchal rigidity. Vomiting occurred infrequently and was never of the projectile type. The neurological signs also varied. Occasionally there was a suggestion of facial fixity. Scattered, unequal and variable reflexes were described. At times there were a questionable right Babinski and absent right abdominal reflexes. At times there was a definite palsy of the left side including the face and the patient was unable completely to close the left eye. An eye consultant found both discs hazy and the retinal vessels tortuous, especially on the left, indicative of a moderate degree of intracranial pressure probably more localized on the left side.

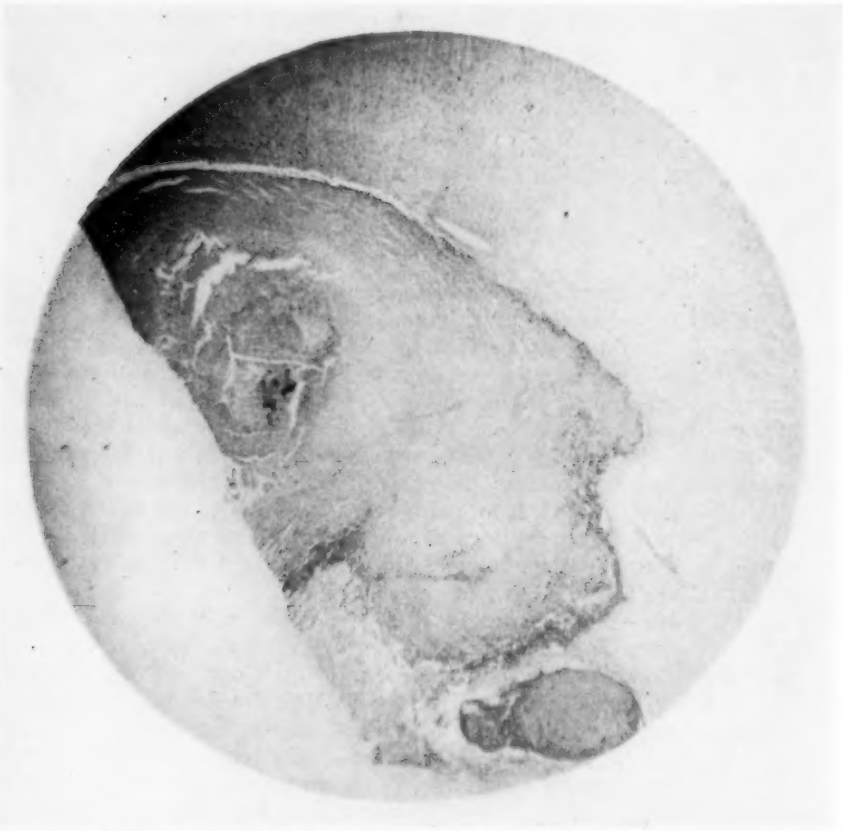

FIG. 1. The cicatricial lesion of the left parieto-occipital cortex.

Spinal taps always relieved the headache and drowsiness, sometimes very quickly. On the last day he became very restless and irrational and resembled a hypomania. Death occurred suddenly.

*Spinal Fluid Findings.* Twenty-one spinal taps were performed. Only once was the fluid somewhat cloudy; on the other occasions it was water-clear. The pressures varied greatly, ranging from 3 to 4 mm. Hg to 46 mm. Usually it lay between 26 and 38 mm. The cell counts were always increased, from 78 on admission, to 340. Lymphocytes predominated, 75 per cent or over. Globulin was always present in traces. Except in the first specimen, sugar was absent. Cultures and

animal inoculations remained negative throughout the entire duration of the disease. Fortunately portions of many of the fluids had been saved in the laboratory, and after the autopsy, the cultures and animal inoculations were repeated. The results were the same.

The temperature curve was of a remittent character, gradually rising from 99° to 102.6° in 10 days, then slowly falling to 98.4° by the middle of April. From then until the end, the fluctuations were greater, more septic in type and reached 103.6°. The pulse was relatively slow and closely paralleled the temperature.

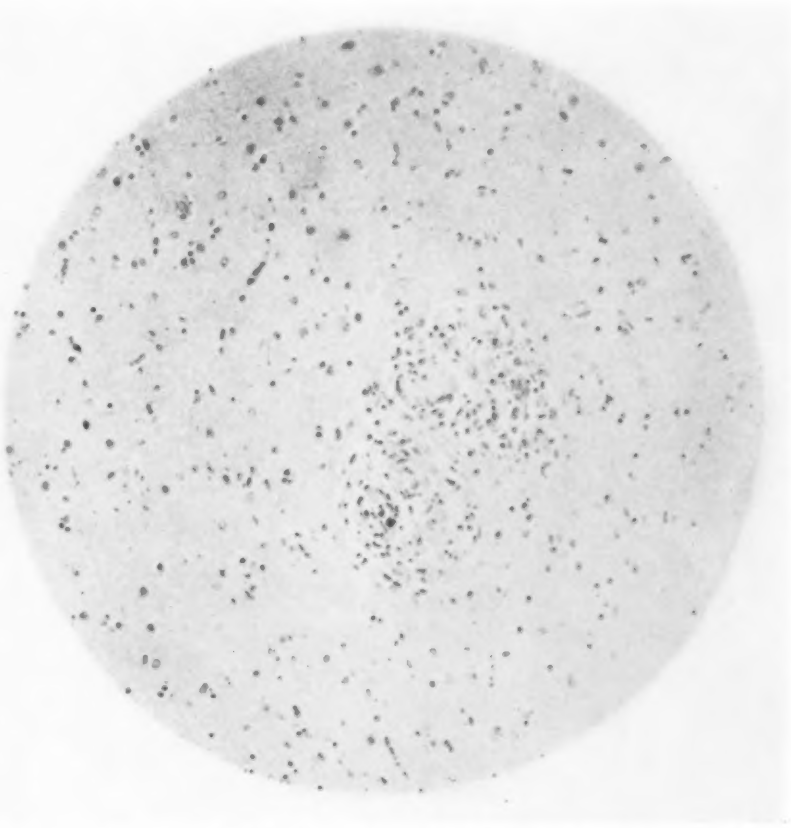

FIG. 2. The more compact lesion of the cerebrum showing the tuberculoid type of reaction. Torula are present within and outside the giant cells.

*Necropsy.* The most prominent feature of the brain was the extreme edema and the enlargement of the right temporal lobe. In the cortex of the left parieto-occipital lobe was a small mass measuring 2 cm. in diameter, densely hard in consistence and resembling a healed tuberculous lesion. Over the base of the cerebrum, pons and medulla, the meninges were finely granular.

On section, the most prominent lesion was found in the region of the basilar nuclei. The entire region appeared completely disorganized by minute necrotic bright yellow foci. The entire brain appeared engorged and edematous.

*Histology.* Sections were taken from the basilar nuclei, parieto-occipital regions, pons, medulla, cerebellum, choroid plexus and gasserian ganglia.

The lesion of the left parieto-occipital cortex was formed by a confluence of dense fibrotic masses with a concentric formation. Some of the masses contained fine calcium deposit. Others had small necrotic centers with numerous polynuclear cells and masses of chromatin. In one region there were torula, apparently undergoing degeneration and staining intensely by the gram technic. At the periphery of the lesion was a compact zone of lymphoid cells and a rare giant cell.

The most extensive lesions were in the regions of the basilar nuclei. They were lytic in nature and contained torula in very large numbers. These lesions

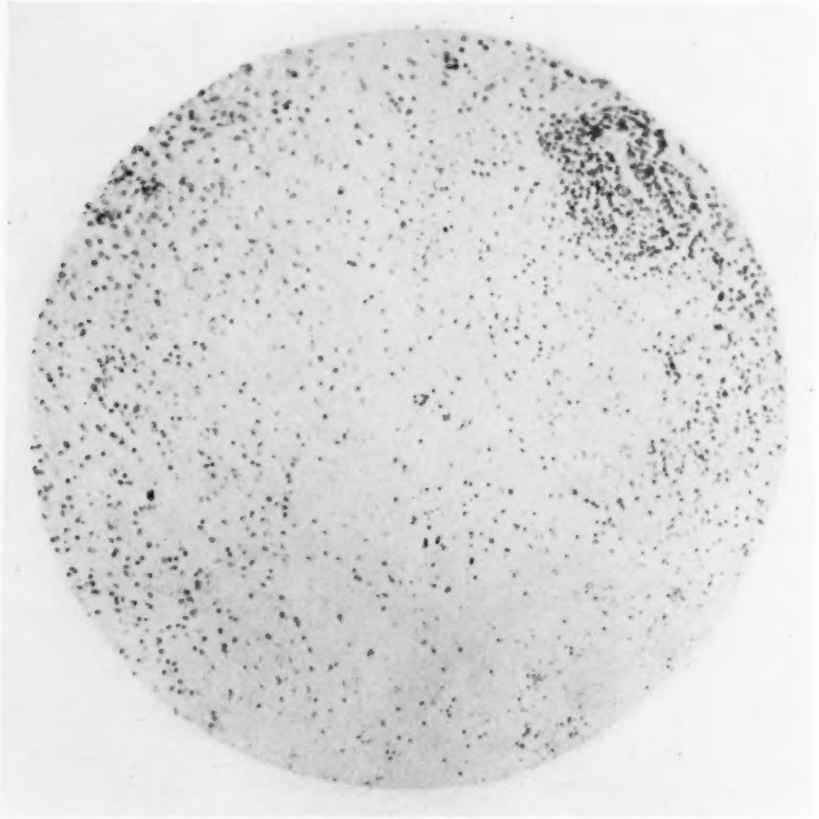

FIG. 3. The more diffuse type of lesion, lytic in nature, showing the complete disorganization of the tissue. Section taken from the basilar ganglia.

were not sharply delimited but involved the tissue diffusely. They merged into a more circumscribed lesion characterized by a tuberculoid reaction. Torula were present in these latter lesions both within and outside the giant cells.

The meningeal involvement was more intense over the pons and medulla than over the base of the brain. It was characterized by a tuberculoid reaction with numerous giant cells. The underlying tissue was involved by extension. Nonspecific areas of degeneration with marked demyelinization were prominent in the medulla.

The lesions of the choroid plexus and gasserian ganglia were similar to those of the meninges.

Torula were present in profuse numbers, either free in the tissues or within giant cells. They were characterized by round, oval or egg shape, a single or double contour, frequently by spiked ends, and by budding. Staining reaction was variable. With hematoxylin and eosin, the capsules stained usually dark or light blue, sometimes with a narrow eosin-stained peripheral zone. With the gram stain, the heavier capsules stained intensely brown, the finer capsules red. The double contour frequently was much sharper with the gram stain than with hematoxylin.

Torula lesions of a tuberculoid nature were found histologically in the kidneys. All the other organs were negative.

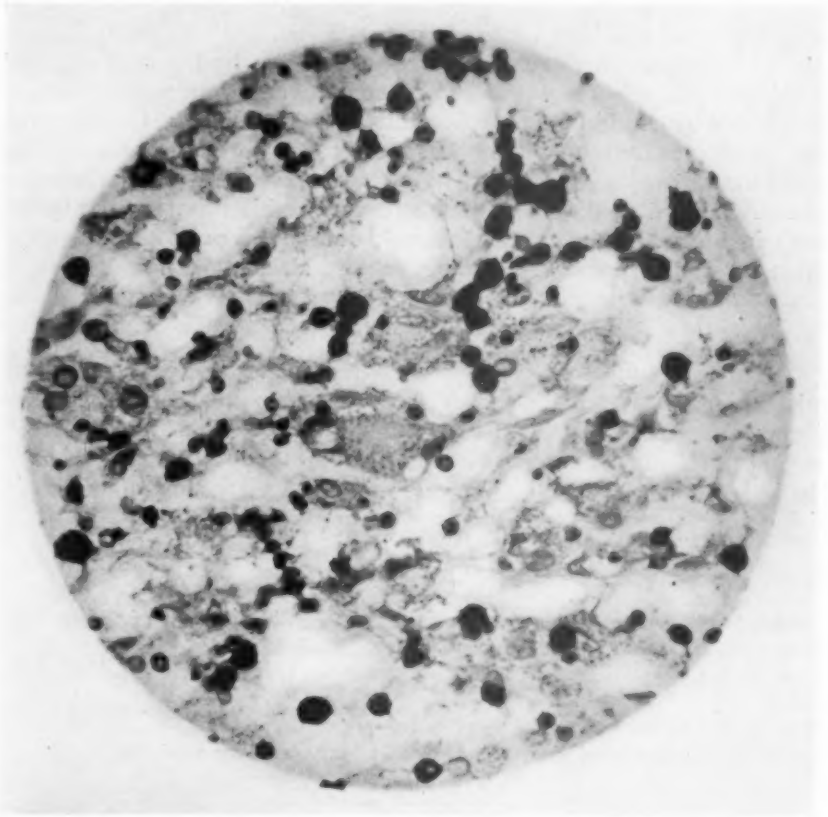

FIG. 4. The same region as figure 3, stained by the gram technic. This view shows the profusion of the organisms, their shape, the variability of reaction to the stain, the spiked ends and the budding.

## COMMENT

The rapid course, the fever and the history of tuberculosis of cervical lymph nodes suggested in this case the diagnosis of tuberculous meningitis. The repeatedly negative results of animal inoculations, however, was a strong point against this diagnosis. Because of them, the possibility of torulosis was en-

tertained. The negative bacteriological results again prevented a correct diagnosis being made. The failure to demonstrate torula in the cerebrospinal fluid is unusual, since most cases are positive, at least late in the disease. That the results were due to discarding the cultures too soon, a point mentioned by Levine, does not apply to this case, since they were kept for a period of one month. The inoculated animals were kept for two months before killing. The first positive evidence was offered by the histological examination. The most acute and youngest lesion was in the meninges.

The chronic cicatrizing lesion of the cortex has hitherto been unreported in the literature. That this lesion is due to torula is proved by the presence of organisms. The odd persistence of the organism has also been observed by Weidman [3] in experimental torulosis in the monkey. Lesions which had spontaneously regressed and been replaced by scar tissue, still had demonstrable organisms. In the present case, the cicatrix appears to be the only explanation of the epileptiform seizures which had occurred over a four year period.

The history of cervical adenitis diagnosed tuberculosis is a further point of interest. Unfortunately no biopsy was performed, so definitive pathology in this gland could not be decided. That it may have been torula infection is possible. A mistake in diagnosis of a cervical adenitis was reported by Wile.[4] Although in his case, Hodgkin's disease had been diagnosed, subsequent examination revealed that the lesion was due to torulosis.


## Summary

A case of torula meningo-encephalitis is reported. There was a history of epileptiform seizures extending over a four year period and a final acute meningo-encephalitic syndrome of seven weeks' duration simulating tuberculosis. The diagnosis of torula infection was made at the postmortem table. The pathological changes revealed all stages of torula infection and included a cicatrizing brain lesion, a hitherto unreported observation.


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# EXANTHEM SUBITUM; REPORT OF A CASE *

By Morgan Cutts, M.D., *Providence, R. I.*

R. C., a white female aged 31, was first seen on February 3, 1937, complaining of general malaise and weakness of one day's duration. Three days previously she had returned from a week's trip to Texas, and had felt quite well until she noted chilly feelings, weakness, some headache and general malaise on February 2. She had no coryza, sore throat, aching in bones or joints, lacrimation, cough, or pain in

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the chest, and she had taken no drugs of any kind recently. She had had both measles and rubella as a child, but not scarlet fever, and the remainder of her past history and family history was non-contributory.

On physical examination her temperature was found to be 102° by mouth, but apart from this there were no abnormal findings. Her throat appeared normal, and a throat culture was subsequently reported negative for hemolytic streptococci.

There were no Koplik spots, and no glandular enlargement. A leukocyte count done later the same day was 3,200 with approximately 50 per cent polymorphonuclears. It was remarked at the time that she was surprisingly free of symptoms, as the slight malaise she had complained of had been completely relieved by 32 mg. of codein and 0.6 gm. of aspirin. Her temperature remained elevated between 100° and 102° for three days, without the development of any other symptoms, after which it suddenly dropped to normal and there appeared at the same time a measles-like rash, in places confluent, over the neck, body, and upper arms. This in turn faded after 24 hours and had completely disappeared in two days. There was no subsequent rise in temperature, and the patient was discharged with a diagnosis of *exanthem subitum*. Several days after recovery her white blood cell count was found to be 7,600.

Zahorsky [1] first clearly described this disease in 1910 and 1913 under the name of *roseola infantum*, and Vieder and Hempelmann [2] in 1921 suggested the name of *exanthem subitum*.

A recent article by Zahorsky [3] clearly describes the typical course of this disease in infants and children. One attack usually confers immunity, and only rare instances of infection of one child by another have been observed. The incubation period is believed to be 8 to 14 days. Fever lasts for approximately four days and falls suddenly, at which time the rash appears, first on the back and abdomen, and rapidly spreads to involve most of the body. Constitutional symptoms, such as restlessness, headache, and gastrointestinal disturbances, may be more or less marked, but are rarely severe. Leukopenia is a constant finding, and affects chiefly the cells of the granular series. No complications have been observed. No previous report of a case occurring in an adult could be found in the literature.

As in the case here reported measles, rubella, and scarlet fever can generally be ruled out fairly easily, especially by the typical time relationship of the fever and rash. The absence of any severe symptoms or of a second rise in fever also speaks against dengue, which was a definite possibility in this case, and is mentioned by Zahorsky as a possible source of error.

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# A CASE OF CARCINOMA OF THE ISLANDS OF LANGERHANS WITH HYPOGLYCEMIA*

By HENRY JOACHIM, M.D., F.A.C.P., and MORRIS M. BANOWITCH, M.D., F. A. C. P., *Brooklyn, New York*

THE syndrome of spontaneous hypoglycemia described by Seale Harris [1] was attributed by him to hyperinsulinism. Since then this conception has been amply confirmed by numerous reports in the literature, and particularly demonstrated by Wilder, Allan, Power and Robertson [2] in 1927. They reported a case of carcinoma of the islands of Langerhans with liver and lymph node metastases, the extract of which was found capable of lowering the blood sugar in rabbits.

In the past 10 years numerous cases of spontaneous hypoglycemia due to tumor formation have been reported but the great majority have been due to hyperfunctioning of adenomas of the islands of Langerhans. Islet carcinoma causing this syndrome has been relatively rare. There have been seven cases (Wilder [2] et al.; Hamdi [3]; Judd, Faust and Dixon [4]; Bickel, Mozer and Junet [5]; Cragg, Power and Lindem [6]; Howland, Campbell, Maltby and Robinson [7]; Graham and Womack [8]). To these we wish to add a case of spontaneous hypoglycemia due to islet carcinoma.

## CASE REPORT

The patient was a female, aged 31, housewife by occupation, who was admitted to the Beth Moses Hospital April 4, 1935 and died May 27, 1935. The chief complaint on admission was of convulsions for the preceding three days, followed by coma eight hours prior to admission.

The family history was essentially negative except that one sister was suffering from encephalitis. Patient had given birth to five children, all living and well.

Eleven years before, following childbirth, she had developed salpingitis from which an uneventful recovery had taken place with no operative interference. Otherwise patient had never been ill.

For the past four years the menstrual periods had been somewhat irregular and she had noticed that her bleeding had increased.

The present illness began three days before admission when suddenly the patient began to sweat profusely. This was followed by convulsions which involved the entire body, and which were followed by comatose periods of varying duration. On awakening she would remember nothing. During the three day period she had numerous such attacks, the last attack commencing at 4 p.m. on the day of admission to the hospital; at 11 p.m. the patient was still in coma.

In checking back the history we received the following information: Four weeks prior to admission the patient had fallen down a flight of stairs and since that time had complained of headaches and had experienced several fainting spells.

On admission the patient was comatose. She was well nourished with some tendency towards obesity. There was no evidence of any cranial nerve palsies; no rigidity of the neck. The heart and lungs were essentially negative; the liver and spleen were not felt. After the patient had come out of coma, there was definite tenderness noted above her umbilicus and somewhat to the left, but no definite masses were palpated.

The temperature on admission was 99.8°, pulse 100, respiration 22. Blood pressure 130 systolic and 70 diastolic. Examination of the urine was negative. The

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blood sugar, taken immediately on admission and before the administration of glucose was 30 mg. per 100 c.c.

A diagnosis of hypoglycemic shock secondary to hyperinsulinism, was made. At that time the possibility of adenoma of the pancreas as an underlying pathological factor was considered.

Intravenous administration of 50 per cent glucose brought the patient out of coma quickly.

For the next two days the patient had no attacks, but, on April 5, at 12:30 a.m., she lapsed into coma. Intravenous glucose was given and the patient responded well. The third attack occurred on April 6, at 6:28 a.m.; the patient again passed into coma, intravenous glucose was given, but the response was not as dramatic as on the first administration. The blood sugar at this time was 25 mg. per 100 c.c. The patient remained in fairly good shape without any attacks until April 11. During this period she received glucose frequently by duodenal tube and in her diet. Her blood sugar remained at 70 mg. Another hypoglycemic attack occurred on April 12 during which her blood sugar fell to 25 mg.

On April 8 a glucose tolerance test was carried out. Specimens were taken every 15 minutes from 10:45 a.m. to 4:45 p.m.

*Sugar Tolerance Test*

| | | | |
|---|---|---|---|
| 10:45 | Blood sugar 120 mg. | (100 grams of glucose were given.) | |
| 11:05 | Blood sugar 125 mg. | 1:10 | Blood sugar 75 mg. |
| 11:20 | Blood sugar 130 mg. | 1:30 | Blood sugar 65 mg. |
| 11:35 | Blood sugar 150 mg. | 2:00 | Blood sugar 65 mg. |
| 11:50 | Blood sugar 65 mg. | 3:15 | Blood sugar 60 mg. |
| 12:05 | Blood sugar 65 mg. | 3:45 | Blood sugar 50 mg. |
| 12:15 | Blood sugar 60 mg. | 4:15 | Blood sugar 70 mg. |
| 12:30 | Blood sugar 60 mg. | 4:45 | Blood sugar 75 mg. |
| 12:50 | Blood sugar 70 mg. | | |

Because of the repeated attacks of coma the patient was transferred to the surgical service for operative interference. On April 15 exploratory laparotomy was performed by Dr. Harold Rabinowitz, and the findings were as follows:

The liver, gall-bladder, stomach and duodenum were normal. Along the lesser curvature of the stomach a hard indurated gland could be felt, the size of a pea. In the terminal half of the pancreas a hard irregular and nodular mass about the size of a tangerine orange and several large glands were palpated. The vessels of the spleen seemed to be buried in the mass at the tail end of the pancreas. The spleen had to be removed in order to get at the mass in the pancreas. Only part of the neoplasm could be removed. The patient's immediate postoperative reaction was good.

The pathological report was as follows:

*Gross:* The specimen consists of a spleen and two small portions of pancreatic tissue. The spleen weighs 170 grams. It is moderately firm and rubbery in consistency and on cross section presents a homogenous reddish-brown appearance. The trabecular markings are distinct. The follicles are indistinct. The masses of pancreatic tissue reveal firm, discretely circumscribed, golden-yellow nodules, ranging from 3 to 7 mm. in diameter. They are firm in consistency, and in the second portion of tissue removed reveal some degree of invasion of the surrounding normal lobules of pancreas, which are of a more grayish-tan color. In this portion of tissue, there is a discretely circumscribed structure, apparently a lymph node, measuring 7 cm. in length, and 1 cm. in diameter. Cross section reveals a pearly-gray appearance with a thin rim of lymphoid tissue surrounding the pearly-gray nodular mass. The portions of tissue removed are too small for biochemical assay.

Nests of polygonal cells with large clear nuclei are present. The latter have well-formed nuclear membranes and contain a nucleolus. The nuclei vary considerably from clear vesicular structures to large hyperchromatic nuclei with coarse

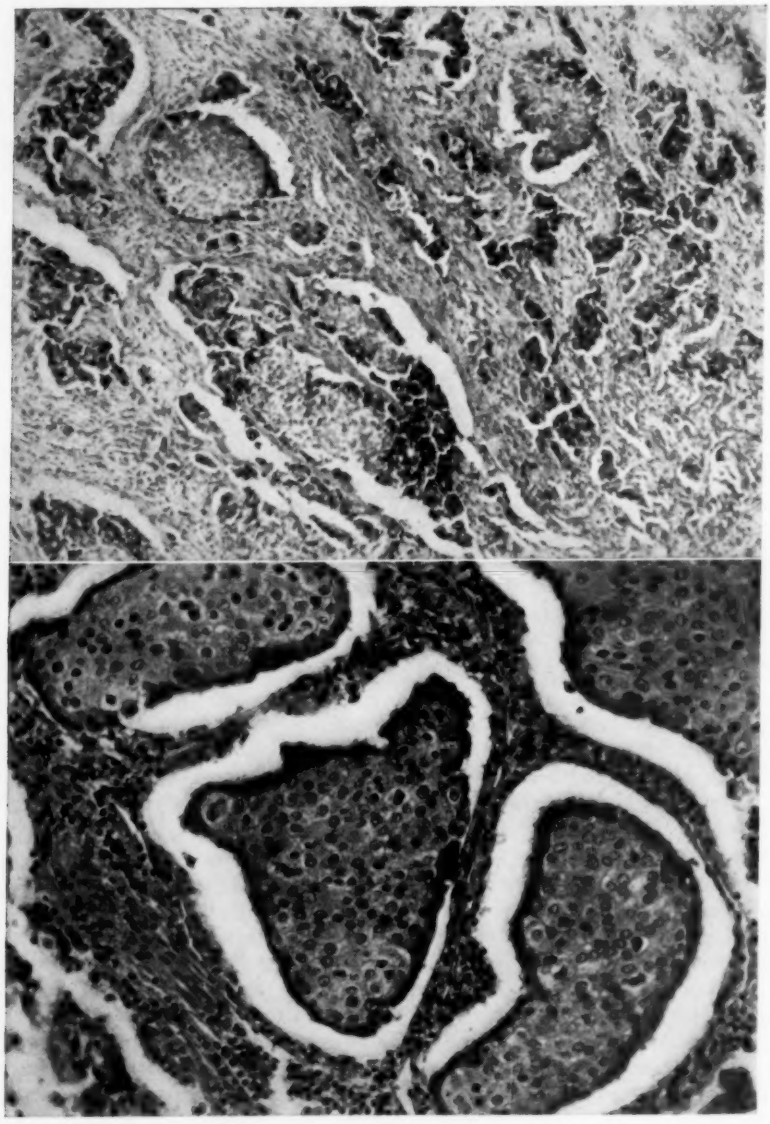

FIG. 1 (*above*). Island cell carcinoma in the pancreas (low power).
FIG. 2 (*below*). Island cell carcinoma in the pancreas (high power).

chromatin clumps. The nests are covered with a layer of syncitial-like cells. Aniline-fuchsin methyl green stains reveal only a few green granules in the cytoplasm, whereas the islets in the normal portion of pancreas contain red and green granules. The cytoplasm is dust-like and contains numerous vesicular structures.

A lymph node contains nests of similar cells.

The spleen reveals sinus hyperplasia and distention. The follicles are somewhat compressed. The sinus reticulum is hyperplastic.

*Diagnosis:* Carcinoma of the pancreas with lymph node metastasis. Chronic passive congestion of the spleen.

For the first four days after operation glucose was administered frequently by duodenal tube and vein. The patient was free from attacks of coma. However, on April 19 another episode of sweating, convulsion and coma took place, and, from then on these attacks kept recurring daily so that on April 29 there were only traces of sugar in her blood. From then on the attacks of sweating and twitching recurred frequently in spite of almost continuous glucose administration. The glucose became less effective and the patient expired May 27.

Additional laboratory findings were: Wassermann and Kahn tests were negative. Her blood count on admission was: Hemoglobin 90 per cent; red blood count 4,100,000; white blood count 15,200; polynuclears 64 per cent; lymphocytes 36 per cent. Prior to her death blood count was as follows: Hemoglobin 50 per cent; red blood count 3,000,000; white blood count 40,000; polynuclears 85 per cent; lymphocytes 15 per cent.

The response to adrenalin injection was as follows:

10:42 Blood sugar 70 mg.
10:45 10 minims of adrenalin was injected
11:01 Blood sugar 60 mg.
11:20 Blood sugar 55 mg.
11:40 Blood sugar 60 mg.
11:50 Blood sugar 55 mg.
12:00 Blood sugar 45 mg.

At this time patient was sweating, apathetic, twitching, and glucose had to be given.

A roentgenogram of the patient's skull revealed the presence of a definitely small sella turcica which was morphologically normal.

The urine was repeatedly negative, except on occasions when traces of sugar were found; probably as a consequence of the glucose injections.

## Discussion

Since the new era in the treatment of diabetes was initiated by the discovery of insulin, the more common use of blood sugar determinations has revealed the frequent presence of a diminution in the normal amount. The normal limits on a fasting stomach vary from 80 to 110 mg. per 100 c.c. of blood, the limits depending upon the method used in the determination. Low blood sugar readings of 70 mg. or less may depend upon an excess of insulin therapeutically administered or spontaneously secreted by the islets of Langerhans. For this latter type Seale Harris coined the name of hyperinsulinemia in 1924. Since then many cases of this condition have been observed. Wilder of the Mayo Clinic was the first in 1927 to establish the causal relationship of tumors of the islet cells, insulomas, to hypoglycemia due to hyperinsulinemia. There are other causes of hypoglycemia not dependent upon structural changes of the islets of Langerhans. From a clinical standpoint a persistent spontaneous hypoglycemia is still not generally recognized by the profession and hypoglycemic states masquerade under the picture of a multitude of diseases.

The normal blood sugar is the balance resulting from the liberation of stored glycogen from the liver into the blood stream as glucose, and the withdrawal of some of this glucose from the blood for tissue deposit and utilization. The difference between the arterial and venous blood sugar is equivalent to that abstracted from the blood for tissue storage or consumption.

Hypoglycemia is present in starvation and states of inanition caused by malignancy, in prolonged fever, excessive vomiting, diarrhea, celiac disease, sprue, extensive hepatic damage, prolonged muscular activity as in forced military marches, Addison's disease, other states of hypoadrenia as after extensive burns, adrenal hemorrhages or toxic adrenal depression as from diphtheria or sepsis, in cases of myxedema, progressive muscular atrophy and myasthenia gravis. In pituitary hypofunction (Simmonds disease) the blood sugar may be extremely low. New-born infants delivered from diabetic mothers may suffer from hypoglycemia as a result of a prenatal compensatory islet hyperplasia to supply the necessary maternal insulin. Hypoglycemia is a characteristic feature of von Gierke's disease.

In discussing the symptoms we are not taking into consideration the acute hypoglycemic states induced by the administration of excessive doses of insulin. We are at present concerned with chronic spontaneous hypoglycemic states.

The most frequent symptom is fatigue and easy exhaustibility, often dissipated by a meal rich in carbohydrates. Extreme hunger, absence of satiation and a constant feeling of emptiness, with a sinking sensation, vertigo, irritability and an excitability resembling that of alcoholism have been observed. Nausea and vomiting may occur. Tremors are often present. The pulse may be rapid and the blood pressure may be low though it is sometimes elevated. Convulsive seizures, diplopia, transient attacks of aphasia and hemiplegia may be due to hypoglycemic states. Hyperhydrosis may occur. Some patients complain of a constant chilliness. Insomnia is a frequent symptom. The first evidence of hypoglycemia may be coma. Attacks of angina pectoris may be precipitated by hypoglycemia. The basal metabolism is low.

## Summary and Conclusions

A case of spontaneous hypoglycemia is reported in which the entire syndrome ran its course in two months. At operation a tumor of the pancreas which proved to be a carcinoma of the islets of Langerhans was found. There were numerous lymph node metastases, and as far as could be determined no metastases of the liver were present. No autopsy was obtained. There were no attempts to demonstrate the presence of insulin in the tumor tissue. However, in view of the cases reported by Wilder et al. and Cragg et al., we believe that we are justified in classifying this case as one due to true hyperinsulinism.

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# EDITORIAL

## *ADVANCES IN THE TREATMENT OF PELLAGRA*

THE success of Goldberger and his associates in experimentally producing pellagra in man and its counterpart, black tongue, in dogs proved that a dietary deficiency plays an essential part in the production of these diseases. His demonstration that yeast, liver, and other foods rich in vitamin $B_2$ (G) prevents and usually cures the disease indicates that the active substance is probably to be found in some portion of the vitamin $B_2$ complex.

Certain facts, however, have led some investigators to believe that other factors are also concerned in the development of the disease. It seems probable that some individual predisposition must exist. The disease, at least in its outspoken forms, appears only in a relatively small portion of a community whose diet seems significantly deficient. Furthermore, a patient with outspoken pellagra may recover without specific treatment while on a diet like that of Goldberger, which is markedly deficient in $B_2$ although it does not lack this entirely. Thus in a series of 107 cases of pellagra reported by Ruffin and Smith,[1] 30 recovered completely while on such a diet before any treatment was given.

The suggestion has been made that there is a lack of some intrinsic factor also in susceptible individuals. Thus Sydenstricker and Thomas[2] believe that there is a deficiency of gastric secretion analogous to, but different from, that found in pernicious anemia. They reported lasting improvement in several patients who were kept on a deficient diet and treated only by the administration of normal gastric juice, and suggested that the effectiveness of the latter was due to the fact that it made possible the efficient utilization of the small amounts of "extrinsic factor" (in the $B_2$ complex) present in the diet.

The injurious effect of exposure to sunlight has also been emphasized.[3] There is no doubt that sunlight may precipitate an attack of pellagra and aggravate the dermatitis, and that it may cause a relapse in inadequately treated patients. However, sunlight alone will not cause the disease, nor will protection from exposure always prevent its development.

The observations of Goldberger justified the hope that relatively simple dietary measures would prove effective in both preventing and curing the disease. Thus far, however, the results obtained are rather disappointing. Although the incidence of pellagra in the United States has diminished, it is still far too prevalent, as is indicated by the mortality rate of over 3000 deaths annually, reported to the United States Public Health Service. Fur-

[1] RUFFIN, J. M., and SMITH, D. T.: A clinical evaluation of the potency of various extracts of liver in the treatment of pellagra, South. Med. Jr., 1937, xxx, 4–14.

[2] SYDENSTRICKER, V. P., and THOMAS, J. W.: Some factors in the etiology of pellagra, South. Med. Jr., 1937, xxx, 14–18.

[3] SMITH, D. T., and RUFFIN, J. M.: Effect of sunlight on clinical manifestations of pellagra, Arch. Int. Med., 1937, lix, 631–645.

thermore, the therapeutic procedures which have been generally employed have not proved successful in the severer cases. Thus Spies, Chinn and McLester [4] reported an average mortality rate of 32 per cent in the Hillman Hospital in Birmingham, Alabama. These unsatisfactory results, however, were probably due in part to inadequate treatment. These investigators were able to reduce the mortality rate in a series of 73 cases of endemic pellagra to 7 per cent by giving larger quantities of food and much larger doses of yeast and liver, provided a sufficient staff of nurses was available to insure that the quantities prescribed were actually consumed.

The effectiveness of liver in the treatment of pellagra has led to the investigation of the therapeutic activity of various types of liver extracts. One of the most careful studies is that of Ruffin and Smith,[1] based on 77 cases who failed to improve while on the basic (deficient) diet. They found that a relatively crude unconcentrated extract for oral administration in pernicious anemia (Valentine's, N. N. R.) was highly potent in curing pellagra, but that the use of concentrated extracts by parenteral channels was definitely less satisfactory. Following the administration of large doses at frequent intervals, in most cases the stomatitis subsided within a few days, and some general improvement followed. Usually, however, either recovery was only partial, or relapse followed quickly after exposure to sunlight. If the oral extract was fractionated by the addition of alcohol, neither the filtrate (which contains most of the pernicious anemia principle) nor the precipitate, if administered individually, gave satisfactory results. The administration of both simultaneously, however, was highly effective. This observation, if confirmed, would indicate that two substances are concerned.

The substance or substances which are required to prevent pellagra are not yet definitely known. Several substances with different physiological properties have been isolated from the vitamin $B_2$ complex. Of these the best known is riboflavin (lactoflavin), a fluorescent dye which plays an important part in the oxidation-reduction reactions in all the body cells. Although a deficiency of this substance causes disease in rats, symptoms due to a deficiency in man have not been recognized, and its administration does not cure pellagra. The same appears to be true of the fraction vitamin $B_6$, lack of which causes a dermatitis in rats; and probably of the "filtrate factor." [5]

In September 1937, Elvehjem et al.[6] reported the isolation of nicotinic acid amide from liver extracts which were effective in curing black tongue in dogs. They found that this substance, as well as commercial preparations

[4] Spies, T. D., Chinn, A., and McLester, J. B.: Treatment of endemic pellagra, South. Med. Jr., 1937, xxx, 18–21.

[5] Jukes, T. H., and Lepkovsky, S.: Distribution of "filtrate factor" (water soluble vitamin belonging to vitamin B complex and preventing dietary dermatitis in chicks) in certain feedingstuffs, Jr. Biol. Chem., 1936, cxiv, 117–121.

[6] Elvehjem, C. A., Madden, R. J., Strong, F. M., and Wooley, D. W.: Relation of nicotinic acid and nicotinic acid amide to canine black tongue, Jr. Am. Chem. Soc., 1937, lix, 1767.

of nicotinic acid, promptly cured the black tongue. This observation led at once to the trial of nicotinic acid in the treatment of human pellagra, and several reports as to its effectiveness are already available. Spies, Cooper and Blankenhorn [7] in November 1937, reported the successful treatment of several cases, and recently [8] have reported the results obtained in 11 cases in all. These investigators (as a rule) kept their patients for one to three days on a deficient basic diet, to exclude a spontaneous improvement, and then treated them with nicotinic acid for one to three days. Subsidence of the glossitis and stomatitis was utilized as evidence of the effectiveness of the treatment, and this was manifested dramatically in every case within 24 to 72 hours. Most of the patients, because of the severity of their illness, were then also given the usual routine treatment for pellagra, so that their observations do not prove how effective nicotinic acid alone would be in curing the other manifestations of the disease. However, Smith, Ruffin and Smith [9] have reported one case, and Fouts et al.[10] have reported four cases of pellagra who were kept on a deficient diet and treated with nicotinic acid alone. Recovery in all cases appeared to be complete and as satisfactory as that obtained with liver extract, except that the dermatitis subsided more slowly.

The dose of nicotinic acid and the mode of administration varied greatly, and within limits appeared to be immaterial. From 0.15 to 1.0 Gm. was given by mouth daily in divided doses, or in some cases from 30 to 60 mg. intravenously or from 50 to 100 mg. by hypodermoclysis. The larger doses caused transient sensations of heat, flushing and tingling of the skin, but no untoward reactions were noted.

The exact relation of nicotinic acid to pellagra has not yet been established, but the evidence strongly suggests that it may prove to be the pellagra-preventive factor of Goldberger. It seems certain to prove a very valuable aid in the treatment of the disease, particularly in the severe cases. Until its effectiveness and its limitations have been more precisely determined, it should be used with due caution, and as a supplement, rather than a substitute for the usual measures of treatment. The cheapness of nicotinic acid would also make practicable its use as a prophylactic measure, if further study shows that it is safe and effective for this purpose.

P. C.

[7] Spies, T. D., Cooper, C., and Blankenhorn, M. A.: Central Society for Clinical Research, Chicago, Nov. 5, 1937.

[8] Spies, T. D., Cooper, C., and Blankenhorn, M. A.: Nicotinic acid in the treatment of pellagra, Jr. Am. Med. Assoc., 1938, cx, 622–627.

[9] Smith, D. T., Ruffin, J. M., and Smith, S. G.: Pellagra successfully treated with nicotinic acid: a case report, Jr. Am. Med. Assoc., 1937, cix, 2054–2055.

[10] Fouts, F. J., Helmer, O. M., Lepkovsky, S., and Jukes, T. H.: Treatment of human pellagra with nicotinic acid, Proc. Soc. Exper. Biol. and Med., 1937, xxxvii, 405.

# REVIEWS

*The Practitioner's Library of Medicine and Surgery.* Supervising Editor, GEORGE BLUMER, M.A. (Yale), M.D., F.A.C.P.; David P. Smith Clinical Professor of Medicine, Yale University School of Medicine; Consulting Physician to the New Haven Hospital. *Supplement and Index Volume.* xliv + 1161 pages, 177 illustrations. D. Appleton-Century Company, Inc., New York. 1938. Price, $10 a volume.

The unnumbered *Supplement and Index* volume, which completes *The Practitioner's Library of Medicine and Surgery,* is the thirteenth in the series. The first of these was given notice in the ANNALS in 1932, and a brief description of each of the succeeding volumes has appeared in these columns. In the present volume the supplemental section comprises 808 pages, and to it 67 authors have contributed. In general, the topics have been arranged in the order of presentation in the preceding volumes with subdivision into sections accordingly. The material presented consists in part of a fuller or modernized treatment of topics already included in earlier volumes. The excellent chapter on The Symptoms, Diagnosis and Treatment of Trichinosis is illustrative of this group. It is a much needed addition to the overly compressed discussion of this subject in Volume III. To a considerable degree the Supplement deals with newer disease concepts, some of which will be found presented here in textbook form for the first time. Meloidosis, Rift Valley fever, onchocerciasis, radium poisoning, calcinosis, glycogenosis, regional ileitis, liver deaths in surgery and the Laurence-Moon-Biedl syndrome are examples of newly defined or recently restudied diseases which are discussed authoritatively. Other important chapters deal with the newer work on the ductless glands and sex hormones, blood chemistry, Boeck's sarcoid, drug reactions, staphylococcic food poisoning, hypoglycemia, pulmonary carcinoma, various hereditary dysplasias, protamine insulin, artificial fever therapy, sympathectomy for vascular disease, sexual impotence in men and the psychological aspects of pediatric practice. To the practitioner with a keen interest in the newer developments in the entire field of Medicine, this volume will prove the most interesting and valuable of the series. The general index, which follows the new textual material, extends over 350 pages. It is not simply a combination of the individual volume indexes but a new compilation, which has made possible a full and logical division of each topic. The reviewer has tested it in various respects and it appears to be unusually adequate. To the supervising editor and his assistants, congratulations are due for the successful completion of the *Library.* It has been a huge task. With the success of the present Supplement in mind, we hope that other supplemental volumes will be forthcoming in order that the *Library* may be kept continuously abreast of the most advanced medical thought of proved value.

C. V. W.

*Diseases of the Skin.* By FRANK CROZER KNOWLES, M.D. Third Edition, thoroughly revised. 640 pages; 16 × 24 cm. Lea and Febiger, Philadelphia. 1935. Price, $6.50.

The author has presented a text whose chief value both to the student and to the practitioner of medicine lies in the excellent clinical descriptions presented of cutaneous diseases, and of those systemic diseases which have cutaneous manifestations. Dr. Knowles has made every attempt to present in a concise manner, in simple

language, a word picture of skin diseases that can be readily understood. He has devoted one chapter to the subject of diagnosis, in which in semi-tabular form he has listed the sites of predilection, and configuration of the commoner skin diseases. The chapter on therapy is an excellent guide in prescribing treatment for patients; radium, roentgen-ray and actino-therapy are all discussed briefly but clearly. The reader is made to feel that dermatology is not a thing apart but that it is an integral part of medicine.

H. M. R., Jr.

*Clinical Laboratory Diagnoses.* By Samuel A. Levinson, M.S., M.D., and Robert P. MacFate, Ch.E., M.S. 877 pages; 14.5 × 23.5 cm. Lea and Febiger, Philadelphia. 1937. Price, $9.50.

The authors have reviewed the pertinent subject matter of anatomy, physiology, biochemistry and pathology at the beginning of each main division of clinical pathology. Such treatment is of necessity too brief and incomplete to be of value for reference though of aid to the student in review. The occasional brief comments on methods of treatment might better have been omitted.

In addition to comprehensive sections on the analysis of gastric and duodenal contents, feces, urine, sputum, blood chemistry, hematology, immunology and serology, spinal fluid, general bacteriological procedures, histological technic, and the metabolism test, there are chapters not often included in similar volumes. These unique sections deal with the laboratory methods in pediatric procedures, legal medicine and toxicology, skin tests and biological tests and a 59-page appendix dealing with the conduct of a course in clinical pathology. This appendix is of value to those interested in teaching the subject.

Few clinical pathology textbooks include such a wide variety of material pertaining to the laboratory. There are very few omissions of important material—the technic for the detection of Bence-Jones protein in the urine being one.

J. H. M.

*Manual of Psychiatry and Mental Hygiene.* By Aaron J. Rosanoff, M.D., University of Southern California. 1091 pages. John Wiley & Sons, New York. 1938. Price, $7.50.

This seventh revised edition is one of the first books on psychiatry to come off the press in 1938, and is surprisingly up-to-date. Recent research in this specialty is presented, and generally accepted views are synthesized into a working manual of diagnosis, prevention, and treatment. The case method is used to clarify each subject discussed.

The volume is divided into six parts. Part I presents the neuropsychiatric syndromes and their etiology. Part II presents in detail the individual pathological conditions found. Part III is devoted primarily to therapeutics, and Part IV to prevention or mental hygiene. Part V gives the various special diagnostic procedures that need to be referred to continually in psychiatric practice, and Part VI gives several supplementary aids, which make the volume complete as a reference book.

This book has stood the test of time, and in this rewritten form the internist will find much valuable advice that he is constantly being called on for. Psychiatry has made many developments during the past ten years, and Rosanoff appears to have missed nothing.

J. L. McC.

*A Method of Anatomy.* By J. C. Boileau Grant, Professor of Anatomy in the University of Toronto. lxvii + 650 pages. William Wood & Co., Baltimore. 1937. Price, $6.00.

There are no textbooks of human anatomy in English which combine adequate descriptive treatment with a clear explanation of mechanical function. All contain details which should enable an experienced anatomist to deduce the functional design of a given part or region; but the treatment is mainly concerned with a description of systemic anatomy, functional analysis of the whole organ or region being confined to generalities in small print. The so-called "applied anatomies" do not meet this need, for they are primarily designed to introduce the surgical approach. For the architectonic principle of structure one must turn to the works of Fick and Braus, which unfortunately are not available in translation.

Professor Grant has perceived this divergence in the modern development of anatomy and has sought to restore the attitude which became prevalent with Borelli's *De motu animalium.* His 'method' is essentially that of regional anatomy as exemplified in a good dissecting manual with the difference that it goes on to clarify the region in terms of functional adjustments. Wherever comparative and developmental anatomy can serve to establish a particular line of evidence they are aptly drawn upon.

The treatment of the acromio-clavicular joint may be quoted in part to illustrate the application of the deductive principle: "The *conoid* and *trapezoid ligaments*, into which the *coraco-clavicular ligment* is subdivided, resist such a force [a fall on, or a blow applied to, the edge of the acromion]; . . . it is their duty to hold the scapula laterally and to prevent it from being driven medially. If this be true, their fibers must obviously pass medially and downwards: which they do. . . . If they are to retain the scapula in position they could obviously take no other direction."

The section on the abdomen, especially with regard to the peritoneal relations of the viscera, is the most comprehensible to be found in an English text. The *situs viscerum* is presented with a clear account of the developmental events leading up to it in a manner quite similar to that of Braus in *Anatomie des Menschen.*

There are 564 line drawings which drive home the deductive principles of the text in a peculiarly forceful way. They make no pretense of being rigidly factual; they serve rather the function of the lecturer's blackboard diagram.

The system of nomenclature used is the Birmingham Revision of B.N.A. with the standard B.N.A. equivalents usually given in parentheses. Whether this feature is an advantage or a defect from the point of view of American anatomy remains for the future to say.

On the whole the book is to be highly recommended for teachers and students alike. It can not be considered in any way to supplant the standard reference texts, but can be used with them as a valuable adjunct to acquiring a conception of the human organism as a whole.

J. C. L.

*The Colon as a Health Regulator—From a Surgeon's Point of View.* By Sir Henry M. W Gray, K.B.E., C.M.G., LL.D. (Aberdeen), M.B., C.M. (Aberdeen), F.R.C.S. (Edinburgh). 100 pages; 13 × 20 cm. The Macmillan Company of Canada, Ltd., Toronto. 1936. Price, $2.50.

The author subscribes to and enlarges upon the thesis that colonic stasis, stagnation and putrefaction, the consequence of bands, kinks, adhesions and other abnormalities are frequent causes of vague abdominal symptoms and chronic ill-health.

Many patients, so ailing but giving none of the manifestations of the more obvious abdominal diseases, are in reality suffering from definite organic lesions, the presence of which most surgeons do not suspect, much less operate upon. Gray accepts in part the speculations of Lane but advances the hypothesis that most if not all kinks and adhesions are developmental abnormalies, the result of faulty descent of the cecum with irregular and imperfect fixations of the large gut. Cause and effect were confused by the older theorist.

The symptoms are many and varied, ranging from constipation, abdominal pain, nausea and vomiting to loss of weight, anemia, acneiform eruptions, nervous and "rheumatic" manifestations. The diagnosis is arrived at by the elicitations of some quite unusual and unorthodox physical signs.

The correction of the condition is accomplished by means of an unusual operation termed a "spring-cleaning" which combines the releasing of kinks and adhesions with the fixation of abnormally mobile portions of the large gut through a long laparotomy incision, done according to the author's formula. Justification for and recommendation of this operation form the main theme of the monograph.

Difficulty in preoperative recognition and selection of suitable cases may cast some doubt upon the desirability of routine adoption of such a procedure. Although there is a very low mortality rate and evidence of some immediate benefit, more convincing proof of its efficacy could be arrived at by a long follow-up of cases, which is not supplied.

M. E.

# COLLEGE NEWS NOTES

## Gifts to the College Library

Grateful acknowledgment is made of the receipt of the following donations to the College Library of publications by members:

### *Books*

Dr. Jacob Gutman (Fellow), Brooklyn, N. Y.—1st Second Series, Supplement to "Modern Drug Encyclopedia";
Dr. Johannes M. Nielsen (Fellow), Los Angeles, Calif.—"Agnosia, Apraxia, Aphasia";
Dr. David Riesman (Fellow), Philadelphia, Pa.—"High Blood Pressure and Longevity and Other Essays";
Dr. T. H. Shastid (Fellow), Duluth, Minn.—"Light, The Raw Material of Vision."

### *Reprints*

Dr. Victor W. Bergstrom (Fellow), Binghamton, N. Y.—1 reprint;
Dr. Oscar Costa-Mandry (Fellow), Santurce, P. R.—2 reprints;
Dr. A. Morris Ginsberg (Fellow), Kansas City, Mo.—3 reprints;
Dr. John L. Goforth (Fellow), Dallas, Tex.—1 reprint;
Dr. Maurice Kovnat (Fellow), Staten Island, N. Y.—1 reprint;
Dr. Johannes M. Nielsen (Fellow), Los Angeles, Calif.—19 reprints;
Dr. William H. Ordway (Fellow), Mount McGregor, N. Y.—4 reprints;
Dr. Ellen C. Potter (Fellow), Trenton, N. J.—1 reprint;
Dr. Harold W. Potter (Fellow), Newport News, Va.—2 reprints;
Dr. John C. Ruddock (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Osborne A. Brines (Associate), Detroit, Mich.—4 reprints;
Dr. Lucien Y. Dyrenforth (Associate), Jacksonville, Fla.—2 reprints, 1 journal;
Dr. Marcos Fernan-Nunez (Associate), Milwaukee, Wis.—1 reprint;
Dr. Hyman I. Goldstein (Associate), Camden, N. J.—3 reprints;
Dr. Donald E. Griggs (Associate), Los Angeles, Calif.—4 reprints;
Dr. Enrique Koppisch (Associate), San Juan, P. R.—1 reprint;
Dr. Charles E. Lyght (Associate), Northfield, Minn.—2 reprints;
Dr. Abraham S. Rubnitz (Associate), Omaha, Nebr.—5 reprints;
Dr. Frederick W. Williams (Associate), New York, N. Y.—1 reprint.

Acknowledgment is also made of the receipt of a copy of the new "Navy Directory," January 1, 1938, from the Bureau of Medicine and Surgery, and of a reprint, "A Portrait Gallery of Physicians—The Collection in the Army Medical Library," by Col. Harold Wellington Jones (MC), U. S. A.

Acknowledgment is also made of a gift to the College Library of a book of poems by Emilie Conklin, Indianapolis, Ind., entitled, "Doctors, I Salute!".

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## New Life Members

The following Fellows have been entered, upon their subscriptions, as Life Members of the American College of Physicians, at the dates indicated, making a total of ninety-eight.

Dr. Charles Ricksher, Norwich, Conn., February 1, 1938
Dr. Floyd H. Lashmet, Petoskey, Mich., February 11, 1938
Dr. John Paul Ritchey, Missoula, Mont., February 14, 1938
Dr. James F. Churchill, San Diego, Calif., February 14, 1938.

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### Committee on Graduate Education and Internal Medicine

In accordance with directions embodied in the following resolution of the Board of Regents, December 12, 1937, Dr. J. H. Means, President, has appointed the following Committee:

"*Resolved*, that the Board of Regents authorize the appointment of a committee by the President of a size which he may select, not necessarily confined to members of the Board of Regents, but to be designated as a committee of the Regents, on the whole question of graduate education and internal medicine."

Dr. William J. Kerr, San Francisco, Chairman
Dr. Charles H. Cocke, Asheville
Dr. Hugh J. Morgan, Nashville
Dr. Charles S. Burwell, Boston
Dr. Joseph A. Capps, Chicago

It is intended that this committee shall supervise graduate courses in medicine arranged by the College for its members, and that the committee will also collaborate with other national committees, when and if its advice and assistance may be called for.

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### Charles Godwin Jennings Memorial Lecture

The First Annual Charles Godwin Jennings Memorial Lecture was held January 27, 1938, under the auspices of the Staff of the Charles Godwin Jennings Hospital. Following dinner at the Detroit Club, Dr. A. F. Jennings (Fellow), President of the Board of Trustees and of the Medical Staff, presided at the meeting. Brief addresses in memory of Dr. C. G. Jennings (Master, deceased) were given by Dr. H. R. Carstens (Fellow), Mr. James Turner, Trustee of the Hospital, and Dr. L. J. Hirschman (F.A.C.S.), who introduced the speaker of the evening, Dr. Walter C. Alvarez (Fellow) of Rochester, Minn. Dr. Alvarez delivered an address on "Origins of Modern Medicine."

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### Regional Meeting of Kentucky Members

About fifty Fellows and Associates of the American College of Physicians resident in Kentucky held their annual meeting and dinner in Louisville under the Governorship of Dr. C. W. Dowden, February 16, 1938. Dr. J. Murray Kinsman was in charge of arrangements. The following program was given at the Louisville City Hospital: "The Insulin Treatment of Dementia Praecox," Spafford Ackerly; "The Diagnostic and Therapeutic Uses of the Bronchoscope," Maurice Buckles; "The Gastroscope as a Diagnostic Agent in Diseases of the Stomach," Sam Overstreet; "Demonstration of the Photo-Electric Colorimeter," John Walker Moore; "The Dying Heart," Virgil Simpson.

In the evening a dinner meeting was held at the Pendennis Club, at which Dr. James H. Means, President of the College, was the guest of honor.

Dr. R. A. Hare (Fellow), formerly of the Staff of the Santa Barbara Cottage Hospital, Santa Barbara, Calif., has been appointed Medical Director of the Washington Sanitarium and Hospital, Washington, D. C.

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Dr. August A. Werner (Fellow), St. Louis, addressed the Sioux Valley Medical Association, Sioux Falls, S. D., January 18, on "Anterior Pituitary-Gonad Relationship in the Female."

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Dr. Louis F. Bishop, Jr. (Fellow), New York City, addressed the Rutgers Medical Club January 27 at New Brunswick, N. J., on "Coronary Artery Disease."

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Dr. William D. Weis (Fellow), Crown Point, Ind., has been reappointed county health commissioner of Lake County, Indiana, for four years. He is the only full-time county health commissioner in that State.

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Dr. J. C. Geiger (Fellow), Director of Public Health of the City and County of San Francisco, has been granted the decoration, "Cruz de Caballero de la Orden del Merito," by the Government of Chile, for his "good friendship and assistance to that country and for his excellent work in and outstanding contributions to public health."

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At a Gastro-Enterologic Symposium held by the Northern Medical Association of Philadelphia (Pa.), January 17, Dr. Anthony Bassler (Fellow), New York, presented a paper on "Etiology, Symptomatology, and Medical Treatment"; Dr. Henry A. Rafsky (Fellow), New York, on "The Relation of the Anemias and Blood Dyscrasias to Disorders of the Gastrointestinal Tract in Adults." Dr. T. Grier Miller (Fellow), Philadelphia, was the commentator.

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Dr. Robert M. Moore (Fellow), Indianapolis, Ind., was elected President of the Indianapolis Medical Society for the year 1938, at its meeting December 7, 1937.

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Dr. Philip I. Nash (Fellow), Brooklyn, has been made President-Elect of the Kings County (N. Y.) Medical Society.

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Dr. Carll Mundy (Fellow), Toledo, Ohio, has been honored by being elected the President-Elect of the Academy of Medicine of Toledo and Lucas County. Dr. Mundy will serve as President-Elect for 1938 and will assume the Presidency in 1939. He is also Chairman of the Advisory Board of Health for Toledo, which board counsels with the City Manager and the City Director of Health in matters of local health policy and health administration. In addition to these activities, Dr. Mundy is Director of Medicine at Lucas County Hospital.

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At the Thirty-Fourth Annual Congress on Medical Education and Licensure held in Chicago February 14 and 15, the following Fellows of the College participated:

Dr. Willard C. Rappleye, Dean of Columbia University College of Physicians and Surgeons and President of the Advisory Board for Medical Specialties, "The Functions of the Special Examining Boards";

Dr. Burrell O. Raulston, Professor of Medicine, University of Southern California School of Medicine, Los Angeles, "An Introduction to Clinical Medicine and Some Variations in the Curriculum of the Third and Fourth Years in Medical School";

Dr. J. G. FitzGerald, Director of the School of Hygiene and Connaught Laboratories, University of Toronto, "Undergraduate Instruction in Preventive Medicine";

Dr. J. H. Musser, Professor of Medicine, Tulane University School of Medicine, New Orleans, "Graduate Medical Education for the Internist";

Dr. James D. Bruce, Director of the Department of Postgraduate Medicine of the University of Michigan, Ann Arbor, "Continuing Professional Education."

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Dr. Hyman I. Goldstein (Associate), Camden, N. J., was elected Vice President of the Northern Medical Association of Philadelphia (founded in 1846) for 1938. Dr. Goldstein was also elected a corresponding member of the Hungarian Dermatologic Association, Budapest, Hungary, as recently confirmed by the Royal Minister of Internal Affairs of the Hungarian Government.

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The cornerstone of the new diagnostic clinic at the Boston Dispensary, Boston, Mass., was laid during December and dedicated to Dr. Joseph H. Pratt (Fellow), Professor of Clinical Medicine at Tufts College Medical School. The building is to be known as the Joseph H. Pratt Diagnostic Hospital. The cornerstone was laid on Dr. Pratt's sixty-fifth birthday. The building was made possible by recent gifts of William Bingham, 2d, because of his interest in providing a medical center at which the development of rural medicine may be planned and supervised.

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Dr. Anton J. Carlson (Fellow), Professor of Physiology in the University of Chicago, is a member of the editorial committee of the "Annual Review of Physiology," in which it is proposed to review developments of each year or biennium in the major fields of physiologic research.

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A recent announcement by the Advisory Board for Medical Specialties states that a Commission on Graduate Medical Education has been created "to mobilize current opinion as to how the problems in this field can best be solved and to formulate the educational principles involved in graduate medical training." The president of the board, Dr. Willard C. Rappleye (Fellow), New York City, appointed four members of the board to form the Commission. Among members of the Commission are the following Fellows: Dr. James D. Bruce, Ann Arbor; Dr. Anton J. Carlson, Chicago; Dr. Reginald Fitz, Boston; Dr. Willard C. Rappleye, New York; Dr. Harold L. Rypins, Albany; Dr. Alfred Stengel (Master), Philadelphia; and Dr. John B. Youmans, Nashville.

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Dr. Waller Smith Leathers (Fellow), Dean of Vanderbilt University School of Medicine, Nashville, Tenn., was selected as the speaker on medical education before a series of educational symposiums, which marked the formal inauguration exercises of Rufus Carrollton Harris, LL.D., as the tenth president of Tulane University of Louisiana, New Orleans, during January. Dr. C. C. Bass (Fellow), Dean of the medical school at Tulane, presided.

A library on tuberculosis, named in honor of the late Dr. Luther F. Warren (Fellow, deceased), was dedicated recently at a memorial service held for Dr. Warren at the Brooklyn Home for Consumptives, of which Dr. Warren was the medical director from 1932 until his death during January, 1937. Dr. Warren was for a number of years very active in the American College of Physicians, being the Governor of the College for eastern New York and later a member of the Board of Regents and of the Committee on Credentials. He was Professor of Medicine at Long Island College of Medicine and Physician-in-Chief to the Long Island College Hospital.

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Dr. Asher Yaguda (Fellow), Newark, N. J., has been elected President of the newly organized New Jersey Society of Clinical Pathologists.

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Dr. Fred M. Smith (Fellow and Governor of the College for Iowa), Professor of the Theory and Practice of Medicine in the State University of Iowa College of Medicine, Iowa City, has been appointed the new Editor of the *American Heart Journal,* succeeding Dr. Lewis A. Conner (Fellow), Professor of Clinical Medicine at Cornell University Medical College, New York, who has retired. Among the new associate editors is Dr. Irving S. Wright (Fellow) of New York City.

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Dr. Russell S. Anderson (Associate), until recently a member of the staff of the Michigan State Sanatorium, Howell, Mich., has been appointed Superintendent of a new hospital for the treatment of tuberculosis in Erie County, near Erie, Pa.

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In connection with a three-day ceremony marking the inauguration of Oliver C. Carmichael, LL.D., as Dean of the Graduate School and Senior College of Vanderbilt University, Nashville, Tenn., the following Fellows participated in the symposium devoted to Medicine:

Dr. William D. Cutter (Fellow), Secretary, Council on Medical Education and Hospitals, American Medical Association, "Trends in Premedical and Medical Education";

Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service, Washington, D. C., "A Forward Look at National Health";

Dr. Wilburt C. Davison (Fellow), Dean of Duke University School of Medicine, Durham, N. C., "A Survey of Medical Education in the South."

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Dr. Ernest E. Irons (Fellow), Clinical Professor of Medicine and formerly Dean, Rush Medical College, Chicago, delivered a public lecture on "The Problem of Arthritis and Its Causes" at the Goodman Theater January 23, under the auspices of the Chicago Medical Society.

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Dr. Paul A. O'Leary (Fellow), Rochester, Minn., has been elected Vice President of the newly formed American Academy of Dermatology and Syphilology. Dr. Samuel Ayers, Jr. (Fellow), Los Angeles, and Dr. Everett S. Lain (Fellow), Oklahoma City, were elected to its Board of Directors.

Among the speakers at the fifty-third annual session of the Mid-South Post Graduate Assembly, held at the Hotel Peabody, Memphis, February 15–18, Dr. J. H. Means (Fellow and President), Boston, delivered a paper on "Treatment of Some of the Commoner Medical Emergencies" and Dr. Russell L. Haden (Fellow), Cleveland, delivered a paper on "Treatment of Anemia."

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At the eighth annual conference of the American College of Radiology, held jointly with the Conference of Teachers of Clinical Radiology, at Chicago, February 13, Dr. Byrl R. Kirklin (Fellow), Associate Professor of Radiology, University of Minnesota (Mayo Foundation), and Secretary of the American Board of Radiology, delivered an address on "The Responsibility of the American Board of Radiology for Setting Up and Maintaining Standards in Radiologic Education." Dr. Benjamin H. Orndoff (Fellow), of Chicago, presented a paper on "The Bedside Manner in Radiology."

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Under the Presidency of Dr. Roscoe L. Sensenich (Fellow), South Bend, Ind., the annual Northwest Regional Conference was held in Chicago February 13, the general subject of the Conference being "Medical Care for all the People." Dr. Herman M. Baker (Fellow), Evansville, Ind., addressed the Conference on "Preventive Medical Care as an Activity of County Medical Societies."

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Dr. Felix J. Underwood (Fellow), Jackson, Miss., has been reappointed as executive officer of the Mississippi State Board of Health.

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Dr. Walter Freeman (Fellow), Washington, D. C., addressed the Missouri-Kansas Neuropsychiatric Association February 15 on "Experiments in Prefrontal Lobotomy in the Treatment of Mental Disorders."

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Dr. John Hamilton Crawford (Fellow), Assistant Professor of Pharmacology and Clinical Professor of Medicine, Long Island College of Medicine, Brooklyn, has been appointed Professor of Clinical Medicine and Director of the Long Island College division at Kings County Hospital.

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On February 9, 1938, Drs. Anthony Bassler (Fellow) and Samuel Weiss (Fellow) of New York City, were decorated by the French Government with the Legion of Honor for their contribution to Medicine and Gastro-Enterology.

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Dr. Joseph H. Barach (Fellow), Pittsburgh, Pa., and Dr. T. E. Newell, Dayton, Ohio, were the guest speakers at the annual banquet of the Stark County Medical Society at Canton, Ohio on Wednesday, February 9, 1938. The subject was: "The Present Status of Medicine in the South American Countries."

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Dr. Clarence E. de la Chapelle (Fellow), Assistant Professor of Medicine at the New York University College of Medicine, is serving as Acting Chairman of the Department of Medicine, pending the filling of the professorship, and as Acting Director of the Third Medical Division at Bellevue Hospital.

## *OBITUARIES*

### DR. SOLOMON LEON CHERRY

Solomon Leon Cherry (Fellow, 1920) died at his home in Clarksburg, W. Va., October 21, 1937 of hypertensive heart disease, which first became manifest in January preceding.

Dr. Cherry was born in Russian Poland, April 10, 1887, and came to America with his parents in 1890. He attended Philadelphia and Baltimore Public Schools and graduated with the M.D. degree from the University of Maryland Medical School in 1908. He interned in Pathology at Bayview Hospital, Baltimore, 1908–09, and was resident in Pathology, Hebrew Hospital, Baltimore, 1909–10. He was Pathologist, Mt. Sinai Hospital, Philadelphia, 1910–13. From 1913–18 he was Pathologist, St. Mary's Hospital, Clarksburg, W. Va. In 1918–19 he served overseas as a captain in the Army Medical Corps, where he was assigned to Evacuation Hospital No. 24 as Chief of the Laboratory Service. After his discharge from the Army in 1919, he returned to Clarksburg as Pathologist, St. Mary's Hospital, which position he held until the time of his death. He was Bacteriologist, City of Clarksburg Health Department, past President and Secretary, Harrison County Medical Society, a member of the West Virginia State Medical Association, of the Southern Medical Association; a Fellow of the American Medical Association; a Fellow of the American Society of Clinical Pathologists; a member of the Catholic Hospital Association, and Secretary of the Medical Advisory Board, St. Mary's Hospital, Clarksburg.

Dr. Cherry was always a student, earnest and hard-working, but rather retiring in disposition. Surviving are his widow and two sons.

WALTER E. VEST, M.D., F.A.C.P.,
Governor for West Virginia.

### DR. GRAYSON EMERY TARKINGTON

Grayson Emery Tarkington, Fellow of the American College of Physicians since 1920, died at Albuquerque, New Mexico, Jan. 12, 1938. Dr. Tarkington was born at Oakland, La. in 1894. He attended Hot Springs high school, Hot Springs, Ark., and graduated from the University of Maryland College of Physicians and Surgeons in 1917. During 1930 he pursued postgraduate work in psychiatry and neurology at the University of Colorado. He was formerly Chairman of the Medical Board, Director of the Out-Patient Department and Visiting Physician to the Leo N. Levi Memorial Hospital, Hot Springs; formerly Chief of the Syphilis Staff of the U. S. Public Health Service Clinic, Hot Springs; also formerly a member of the House Staff of St. Joseph's Infirmary, Hot Springs; formerly

President of the Garland County (Ark.) Medical Society; formerly First Vice President of the Arkansas State Medical Society; Fellow of the American Medical Association; formerly Secretary of the Hot Springs Board of Health; formerly Associate Editor of the American Journal of Syphilis; member of Nu Sigma Nu Fraternity; served during the World War as First Lieutenant, Medical Reserve Corps, U. S. Army; author of many published articles. Because of ill health he removed to Albuquerque, N. M., during 1933, where he became a member of the Staff of the Children's Home and Hospital, Southwestern Presbyterian Sanatorium and St. Joseph's Sanatorium and Hospital.

Dr. Tarkington was not merely a physician; he was a citizen. Many demands were made upon his crowded time by welfare, public health and similar activities, and he never failed to respond. As Director of the Out-Patient Department of the Leo N. Levi Memorial Hospital he was as attentive to its details as to his private practice and much of the present success of this institution is due to his interest in its organization and functioning. His love of medical study induced him to serve as Associate Editor of the *American Journal of Syphilis* without compensation. In this capacity some two hundred medical journals were received monthly from which many of the articles were abstracted, filed and indexed. Few medical men had better command of current medical literature than he. When in 1933 he moved to Albuquerque, his generous and forceful personality was sadly missed in Hot Springs.

WILLIAM H. DEADERICK, M.D., F.A.C.P.,
Hot Springs, Ark.

## DR. CHARLES EASTMOND

Dr. Charles Eastmond (Fellow), of Brooklyn, N. Y., died November 27, 1937, in the Peck Memorial Hospital, of carcinoma of the bladder.

Dr. Eastmond was born in Brooklyn in 1879, and received his medical education at Columbia University College of Physicians and Surgeons, graduating in 1904. Early in his career he determined to follow the specialty of roentgenology, and proceeded to prepare himself along that line. For many years he was roentgenologist to the Carson C. Peck Memorial and the Bushwick Hospitals, and consulting roentgenologist to the Kings County, Long Island College, Jewish, Jamaica and Nassau (Mineola) Hospitals and the Norwegian Lutheran Deaconesses' Home and Hospital. He contributed many papers dealing with roentgenology to medical journals, and was active in many medical societies. He was a member of the Medical Society of the County of Kings, the Medical Society of the State of New York, the Brooklyn Medical Association, the Brooklyn Pathological Society, the Medical Association of Greater New York, the Medical Club of Brooklyn, the Hospital Graduates Club of Brooklyn, Practitioner's Club of Brook-

lyn, the Associated Physicians of Long Island, the American Medical Association, the New York Roentgen Society, the American Roentgen-Ray Society, and had been a Fellow of the American College of Physicians since 1920.

## DR. CHARLES D. VER NOOY

Dr. Charles D. Ver Nooy, of Cortland, N. Y., Associate of the College since March 10, 1923, died January 20, 1938, following a heart attack suffered the night preceding. He had been in poor health for the past year.

Dr. Ver Nooy was born in Accord, Ulster County, New York, February 16, 1868, a descendant of early settlers there. His education was received in the public schools of Ulster County and the Cortland Normal School. For four years he taught school, after which he studied medicine at Syracuse University, graduating in 1892. He opened an office in Enfield, N. Y., but later removed to Cortland in 1898. He early established a reputation for his diagnostic ability and keen observation in the medical field. In his early days his calls were made with horse and buggy. In 1912 he took over the old Cortland Hospital, remodeled it into the Ver Nooy Sanitarium and conducted it as a small hospital and as his private office.

Dr. Ver Nooy was a member of the Cortland County Medical Society, the Medical Society of the State of New York and the American Medical Association. He became an Associate of the American College of Physicians in 1923. Outside of his medical work, he had been a pioneer in the extension of the telephone in his community, having been a Director and President of the old Cortland Telephone Company before its merger with the present system. Dr. Ver Nooy had been a member of the local Board of Education since 1917, and for twenty years had acted as its President. He was a charter member of the City Board of Health, a Director of the Marine Midland Trust Company and Chief of the Staff at the Cortland County Hospital.

C. F. TENNEY, M.D., F.A.C.P.,
Governor for Eastern New York

## DR. LORENA M. BREED

Dr. Lorena M. Breed (Fellow), Pasadena, California, died October 20, 1937. She had been retired from medical practice for some time. Dr. Breed was born at Washington, Iowa, in 1863, received her pre-medical training at the Central University of Iowa and graduated from the Northwestern University Woman's Medical School in 1893. She was early interested in clinical laboratory work. At one time she was connected with the Nalgonda Hospital in India, later returning to California. From 1895 to 1906 she again was in India, and connected with the Hyderabad State Deccan. From 1908 to 1914 she was in charge of the clinical laboratory

of the Pomona (Calif.) Valley Hospital and from 1914, for several years, she was in charge of the clinical laboratory of the Pasadena (Calif.) Hospital.

Dr. Breed was the author of several published articles and of a book entitled " The Human Machine, Its Uses and Abuses." She was a member of the Los Angeles County Medical Society, the California State Medical Society, the American Medical Association and the American Society of Bacteriologists. She became a Fellow of the American College of Physicians on December 30, 1921.